Model studies toward the total synthesis of thebaine by an intramolecular cycloaddition strategy

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ABSTRACT

The present studies describe recent progress toward the synthesis of the thebaine. Model substrates were synthesized using pyridazine derivatives as a starting material, which allowed to assess the key Diels-Alder reaction as a route to construct the thebaine core.

ACKOWLEDGEMENTS

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LIST OF ABBREVIATIONS

Ac	Acetyl
Acac	Acetylacetonate
BTIB	*bis*-(Trifluoroacetoxy)iodobenzene
Bz	Benzoyl
CDI	Carbonyldiimidazole
DBU	1,8-Diazobicyclo[5.4.0]undec-7-ene
DCC	Dicyclohexylcarbodiimide
DCM	Dichloromethane
DIBAL-H	Diisobutylaluminum hydride
DMAP	Dimethylamino pyridine
DME	Dimethoxyethane
DMF	Dimethylformamide
DMS	Dimethylsulfide
DMSO	Dimethylsulfoxide
Dppf	1,1'-Bis(diphenylphosphino)ferrocene
EDC	*N*-(3-Dimethylaminopropyl)-*N´*-ethylcarbodiimide hydrochloride
Et_2O	Diethylether
Et_3N	Triethylamine
HBTU	*N,N,N′,N′*-Tetramethyl-*O*-(1*H*-benzotriazol-1-yl)uranium hexafluorophosphate, *O*-(Benzotriazol-1-yl)-*N,N,N′,N′*-tetramethyluronium hexafluorophosphate
HMPA	Hexamethylphosphoramide

Imid	Imidazole
^{i}Pr	Isopropyl
KHMDS	Potassium hexamethyldisilazide
LAH	Lithium aluminum hydride
LDA	Lithium diisopropylamide
LUMO	Lowest unoccupied molecular orbital
LiTMP	lithium 2,2,6,6-tetramethylpiperidide
m-CPBA	*meta*-Chloroperoxybenzoic acid
Me	Methyl
MsCl	Mesyl chloride
*n*Bu	n-Butyl
NBS	*N*-Bromosuccinimide
*n*Pr	n-Propyl
N_2H_2	Hydrazine
NMR	Nuclear magnetic resonance
nOe	Nuclear Overhauser effect
PAD	Potassium azodicarboxylate
PCC	Pyridinium chlorochromate
Py	Pyridine
TBAF	Tetrabutylammonium fluoride
THF	Tetrahydrofuran
TLC	Thin layer chromatography

TMEDA	Tetramethylethylenediamine
TMS	Trimethylsilyl
Ts	Tosyl
^{t}Bu	Tertiarybutyl
Ph	Phenyl
PPh_3	Triphenylphosphine

I. Introduction

Recently, thebaine has gained increasing notoriety as an important intermediate for the synthesis of other morphinans. An efficient total synthesis could be used to supplement or replace its natural supply. Oxycodone, oxymorphone, naloxone, naltrexone, etorphine, and buprenorphine can all be manufactured through semi-synthesis from thebaine.

The proposed synthesis of thebaine is based on the latent pseudo-symmetry that is present in the target molecule, as shown in Figure 1.

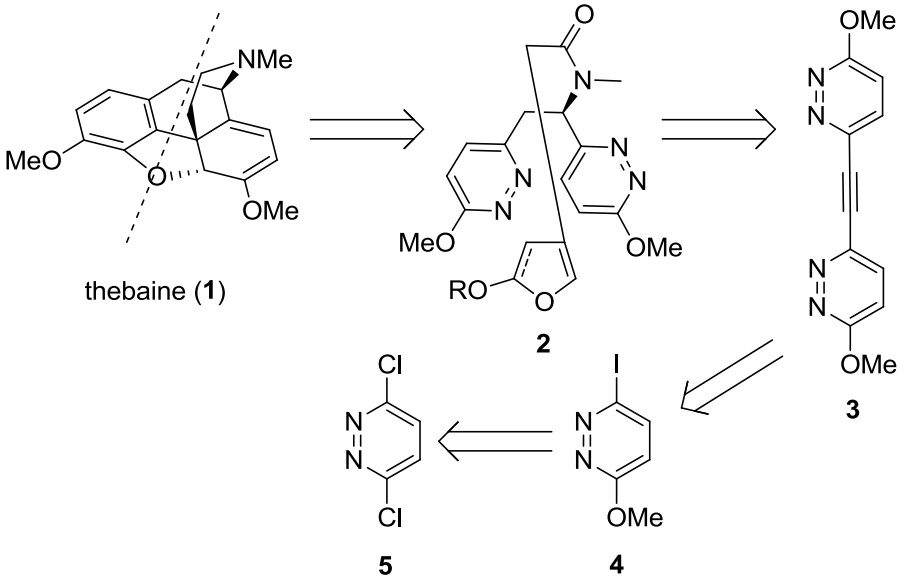


Figure 1. Retrosynthetic analysis for the symmetry-based synthesis of thebaine.

In this thesis model studies will be conducted and the key model compounds **6** and **7** (Figure 2) will be constructed through an intramolecular Diels-Alder reaction. Compound **6** consists of rings D, C and E; and compound **7** consists of rings C and E of the morphine alkaloid core.

In order to determine the viability of the [4+2] reaction, pyridazine derivatives will be used as dienes. An allylic, dihydrofuranyl and furanyl

derivatives will be used as dienophiles for the Diels-Alder reaction, as shown in Figure 2.

Based on the outcome of the initial studies, approaches to the entire core of thebaine will be pursued.

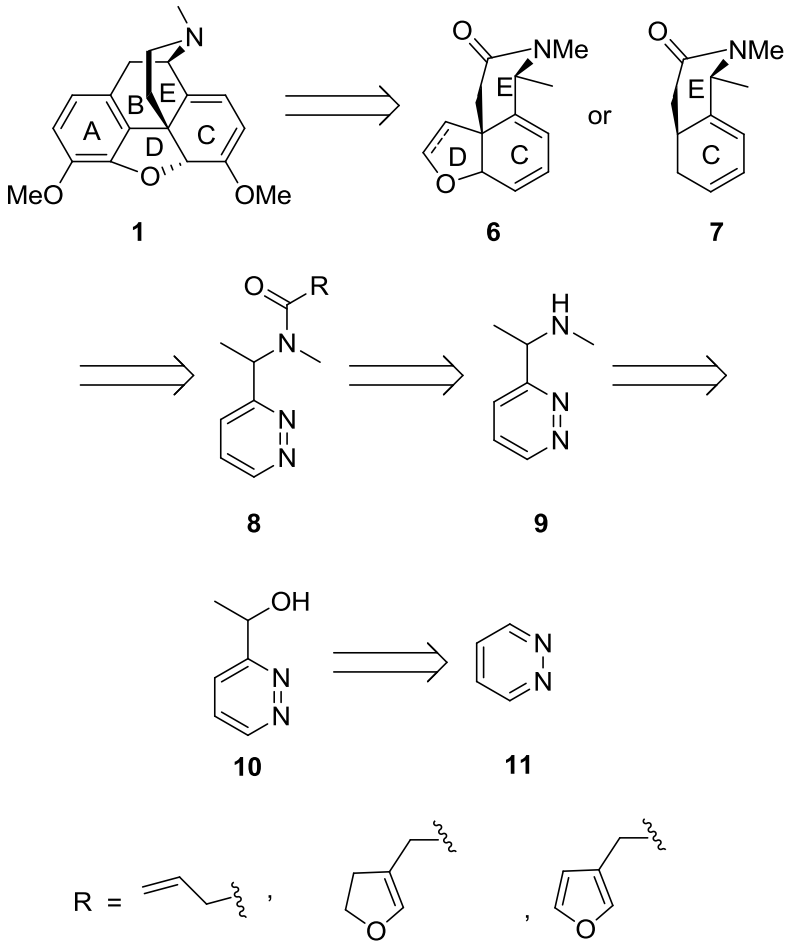
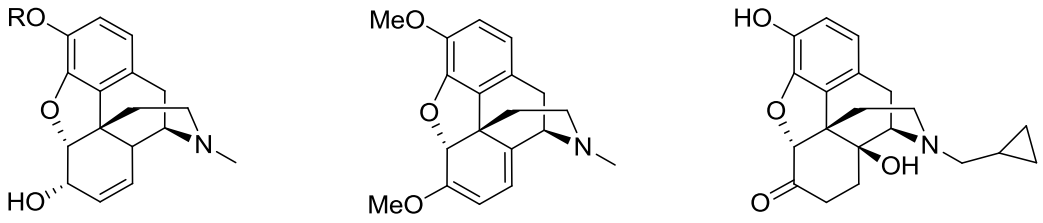


Figure 2. Retrosynthetic analysis for the model studies of thebaine.

II. Historical

II-1 Historical overview, extraction, and biosynthesis of morphine

Morphine and its congeners have attracted the attention of chemists for decades.



morphine, R = H (**12**)
codeine, R = Me (**13**)

thebaine (**1**)

naltrexone (**14**)

Figure 3. Structure of some morphine alkaloids.

Sumerians used opium for the first time in about 3400 BC.[1,2] Serturner isolated the morphine in its pure form in 1805.[3] Laurent disclosed its correct empirical formula, $C_{17}H_{19}NO_3$, in 1847.[4] The phenanthrene core of morphine was confirmed by von Gerichten, when morphine was treated with Zn dust at 300 °C.[5] Later, Hofman and Pshorr confirmed the presence of an oxygenated phenanthrene skeleton from degrading experiments of morphine and codeine.[6,7] Robinson and Gulland proposed the correct structure of morphine in 1925[8] and it was confirmed by Gates in 1952 through his landmark synthesis of morphine.[9]

Opium is isolated from the seed pods of *P. somniferum*. Morphine alkaloids are produced at the certain time of the year therefore time of harvesting opium is important. Seed pods are incised when they ripen and rubb from the surface to collect the latex. This latex contains a number of alkaloids with

morphine as a major constituent. Morphine is isolated from the latex by various methods depending on time and cost.[2]

The biosynthetic summary of morphine starts from the amino acid tyrosine, as shown in Figure 4. Dopamine and 4-hydroxyphenylacetaldehyde are condensed to (*S*)-norcoclaurine from tyrosine by two different pathways. *N*-Methylation, oxidation, and further methylation of (*S*)-norcoclaurine gives (*S*)-reticuline which is epimerized to (*R*)-reticuline. The coupling of the carbon atoms 12 and 13 of (*R*)-reticuline forms salutaridine which is transformed to thebaine in three steps. Demethylation, migration of the double bond, and reduction of the ketone group leads to codeine and further demethylation yields morphine.[10]

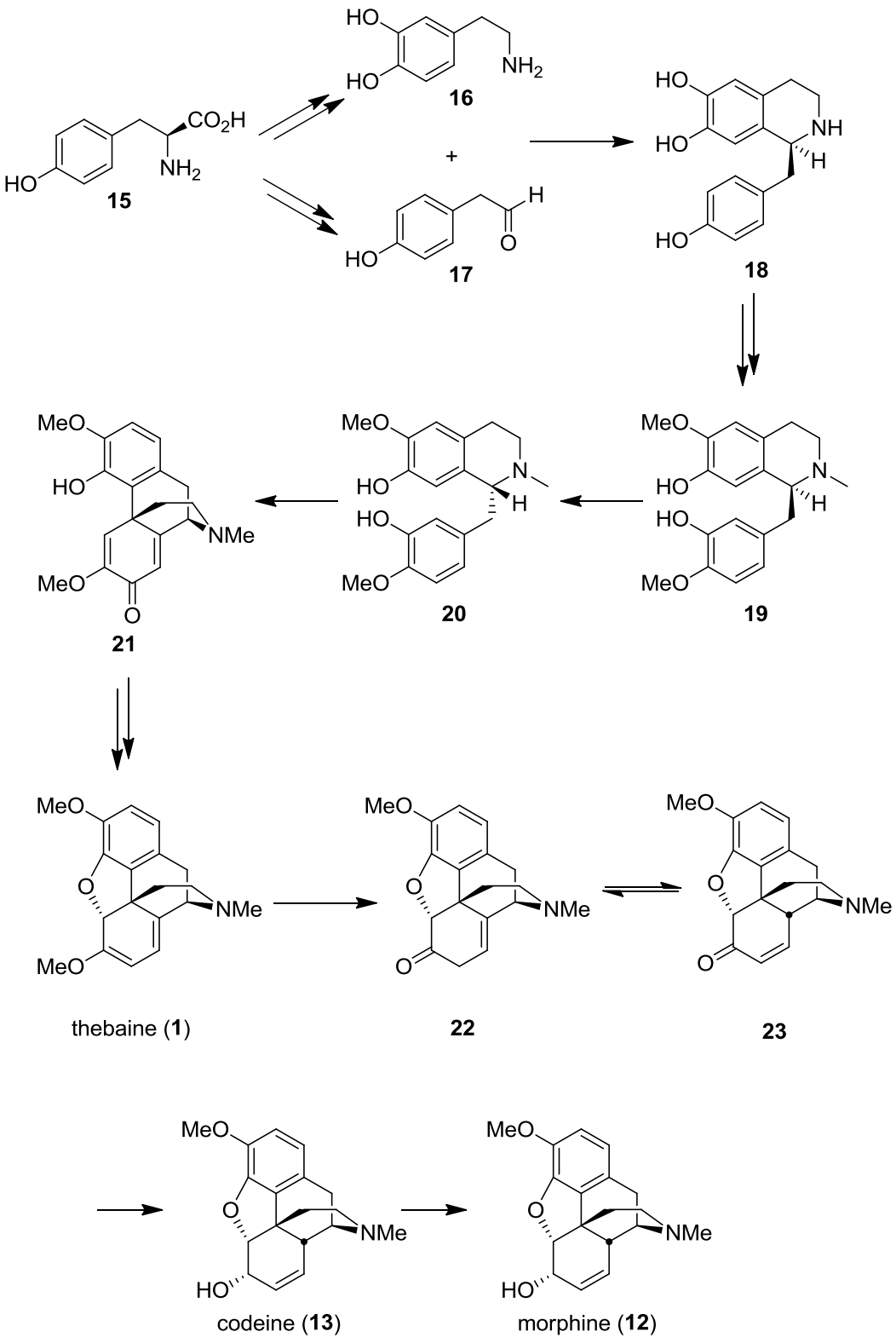


Figure 4. Biosynthesis of morphine alkaloids.

II-2 Morphine Alkaloids: Synthetic approaches by [4 +2] cycloaddition

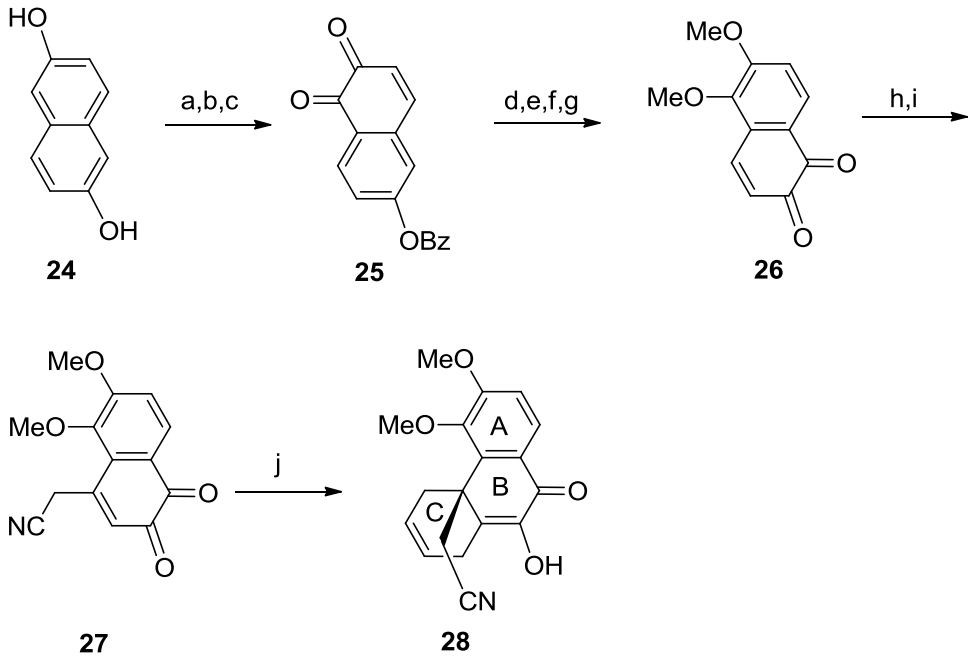
The first total synthesis of morphine was accomplished by Gates in 1952 and since then a number of total syntheses of the morphine alkaloids has been carried out. In the field of morphine synthesis, many synthetic strategies have been developed. One of the most versatile reactions known to organic chemists is the Diels-Alder reaction. It was named after Otto Diels and Kurt Alder, the scientists who discovered this reaction. This discovery led them to win the Nobel Prize in Chemistry in the year 1950. This reaction has been successfully utilized in the synthesis of many complex organic molecules including morphine.

The historical aspects of morphine in terms of the Diels-Alder reaction are summarized below.

Gates (1952)[9]

The total synthesis accomplished by Gates in 1952 used the Diels-Alder strategy, specifically the intermolecular version of the Diels–Alder reaction. The 2,6-dihydronaphthalene **24** was subjected to benzoylation, nitrosation, and reduction to the amino naphthol and was oxidized without the isolation of the naphthoquinone. The quinone was reduced with sulfur dioxide and the catechol unit was converted to its dimethoxy ether. The benzoate was cleaved by treatment with methanolic KOH and the nitrosation-reduction sequence was repeated to attain napthoquinone **26**. A preparative modification of the Craven's test was employed to introduce the cyanoethylacetate functionality into **26** and in a subsequent step the ester was cleaved by Claisen alkali. Compound **27** was one of

the intermediate compounds served as the precursor for the key cycloaddition reaction along with butadiene to construct the C-ring of the morphine skeleton.

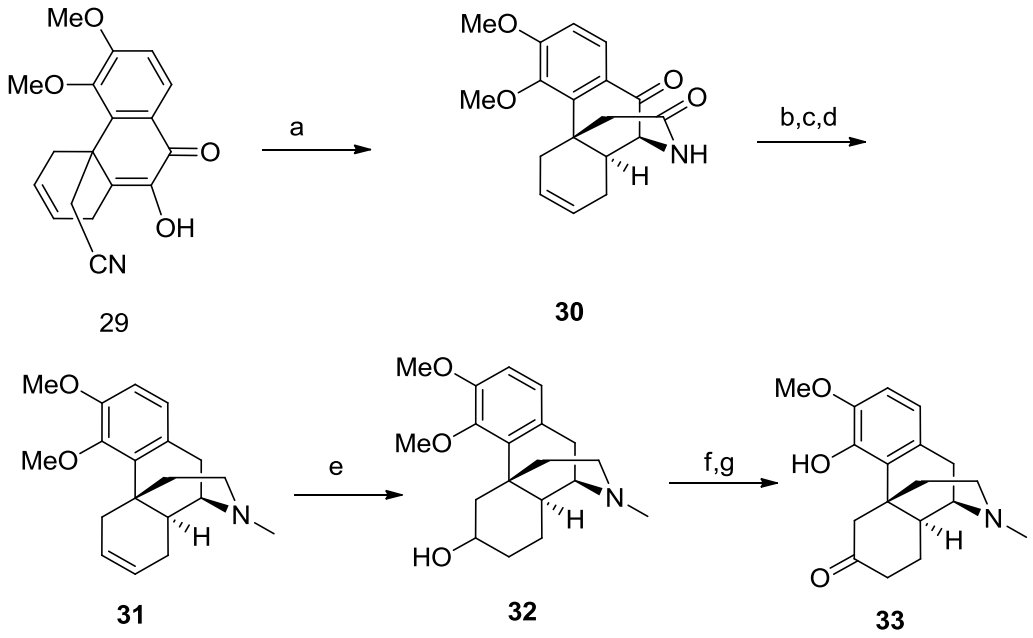


Reagents and Conditions: a) BzCl, py, dioxane (72%); b) $NaNO_2$, AcOH (88%); c) AcOH, Pd(C), H_2, then $FeCl_3$ (85%); d) SO_2, MeOH (91%); (e) K_2CO_3, dimethyl sulphite; f) KOH, MeOH (87%); g) $NaNO_2$, AcOH, Pd(C), H_2, then $FeCl_3$ (82%); h) ethyl cyanoacetate Et_3N, then $K_3Fe(CN)_6$ (84%); i) Claisen's alkali (97%); j) butadiene (66%).

Scheme 1. Gates' Diels-Alder cycloadduct intermediates synthesis.

The D ring of morphine was formed in a rare reductive cyclization reaction mediated by medium-pressure hydrogenation using a copper chromite catalyst at 130 ˚C. Standard Wolff-Kischner reduction of the C-10 ketone followed by alkylation of the amide with iodomethane and resolution with the enantiomorphic dibenzoyltartrate salts yielded structure **31**. Oxygenation at the C-6 centre was accomplished by treatment of **31** with dilute sulfuric acid and

oxidation with potassium *t*-butoxide-benzophenone resulted in ketone derivative **33**.

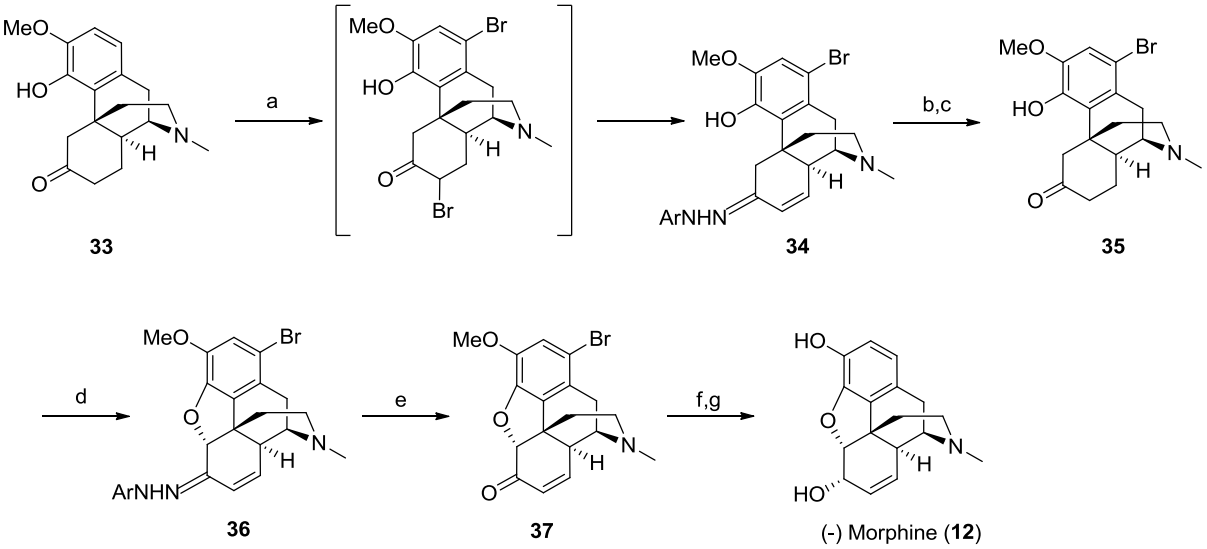


29 **30** **31** **32** **33**

Reagents and Conditions: a) H_2, copper chromite (50%); b) KOH, N_2H_4; c) NaH, MeI; d) LAH (54%) then dibenzoyl tartrate resolution; e) dilute H_2SO_4 (28%); f) KOH, ethylene glycol; g) ^{t}BuOK, Ph_2CO (89%).

Scheme 2. Synthesis of intermediate **33**.

The remaining transformations to morphine mainly consisted of the bromination, hydrazone formation, introduction of the α,β-unsaturation unit, and dihydrobenzofuran ring closure to complete the synthesis of morphine.



Reagents and Conditions: a) Br_2, AcOH, 2,4-dinitrophenylhydrazine (41%); (b) 12N HCl (60%); (c) PtO_2, H_2 (80%); (d) Br_2, AcOH, 2,4-dinitrophenylhydrazine (26%); (e) 12N HCl (27%); (f) LAH (quant); (g) Py•HCl (34%).

Scheme 3. The remaining transformations to morphine.

Ciganek (1981)[11]

Ciganek visualized that a morphine skeleton lacking the B ring could be constructed using a Diels-Alder strategy.

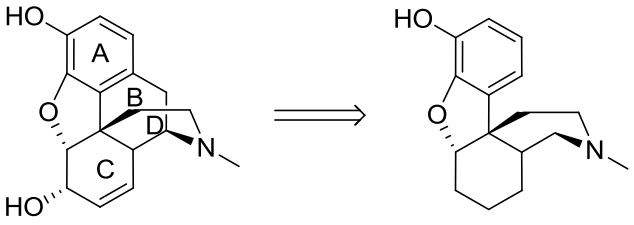
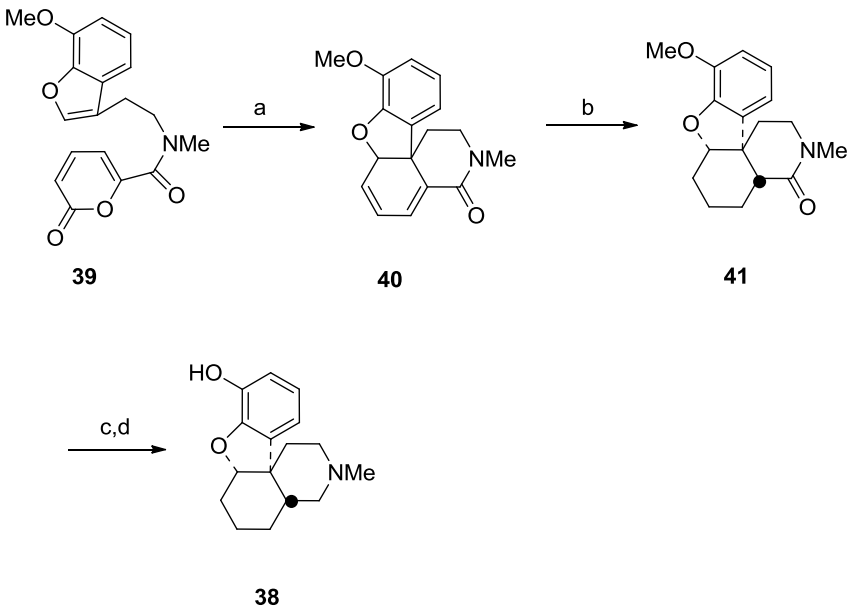


Figure 5. Ciganek's strategy to construct morphine skeleton.

In his unique synthesis benzofuran, as a dienophile, was the first reported application of a benzofuran unit as a dienophile part of a Diels-Alder reaction.

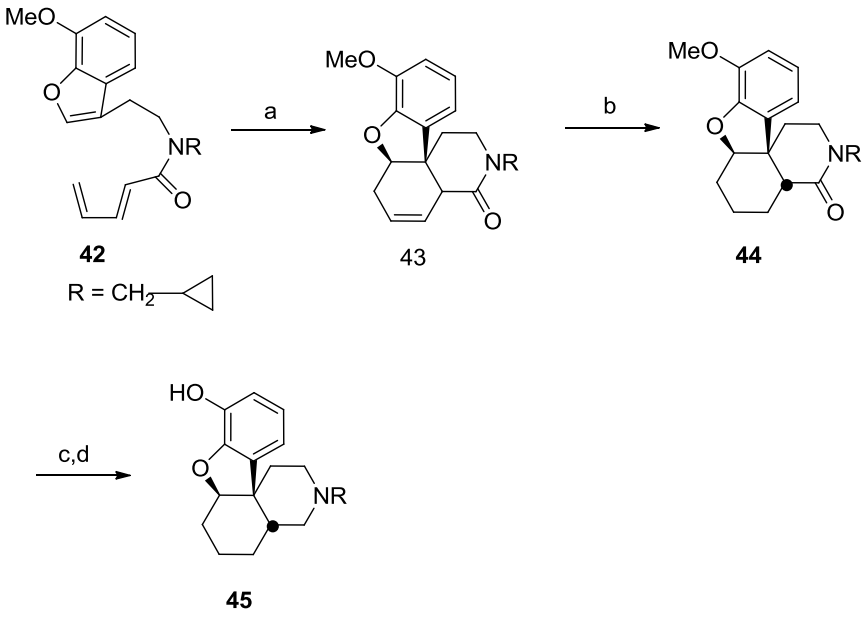
Ciganek synthesiszed **40** from **39** through an intramoleclar cycloaddition reaction which was carried out in 1,2,4-trichlorobenzene at 215°C for 10 h. The cycloaddtion adduct was subjected to hydrogenation and reduction to yield the morphine skeleton with correct stereochemistry.



Reagents and Conditions: a) 215 ˚C; b) H_2, Pd/C; c) BH_3•DMS; d) *n*PrS^-K^+, DMF.

Scheme 4. Ciganek's synthesis of the morphinan skeleton.

At the same time Ciganek also utilized N-(7-methoxy-3-benzofuranethyl)-N-(cyclopropylmethy1) amide of 2,4-pentadienoic acid to construct the morphine skeleton but this time cylcloaddition gave the undesired cycloadduct at 240 °C in toluene.



Reagents and Conditions: a) 240 ˚C; b) H_2, Pd/C; c) BH_3•DMS; d) *n*PrS^-K^+, DMF.

Scheme 5. Ciganek's undesired cycloadduct synthesis of the morphine skeleton.

Tius (1991)[12]

In 1991 Tius visualised that morphine could be constructed from a non aromatic precursor through a Diels-Alder strategy.

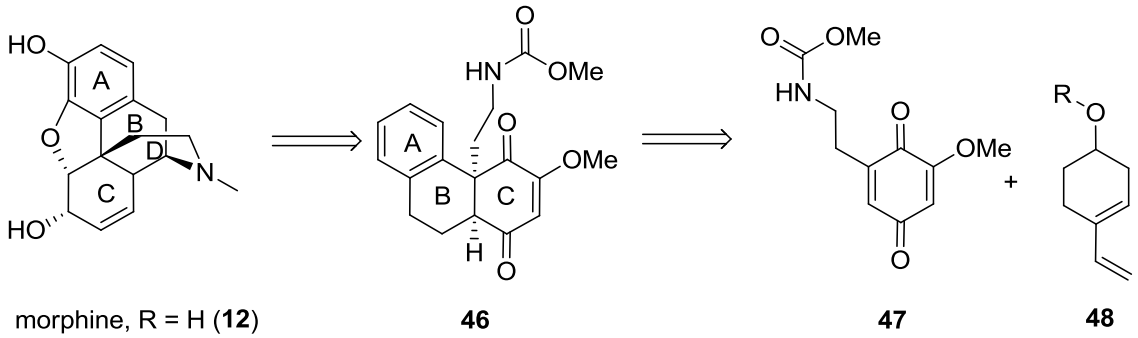
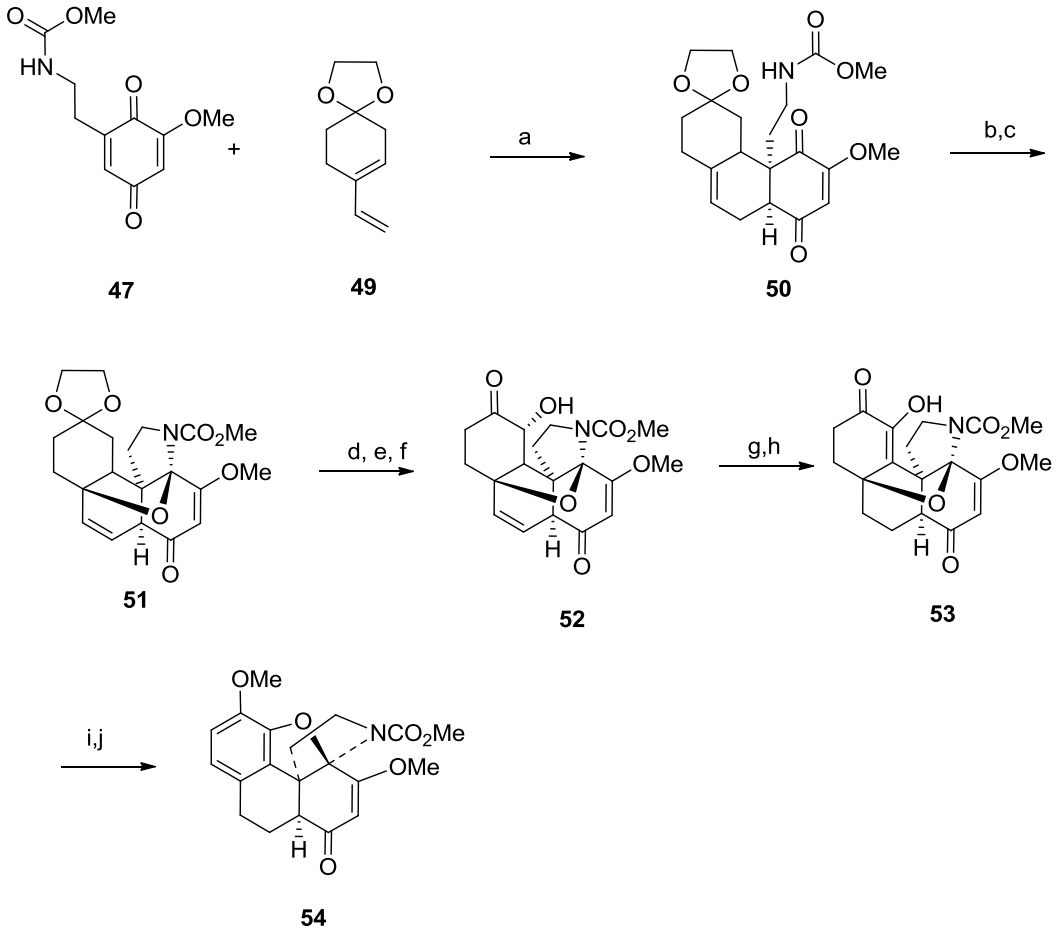


Figure 6. Tius' retro synthetic analysis of the morphine.

He used quinoline and styrene equivalent for a Diels-Alder reaction to construct the A, B and C fused ring of morphine skeleton in a single step.

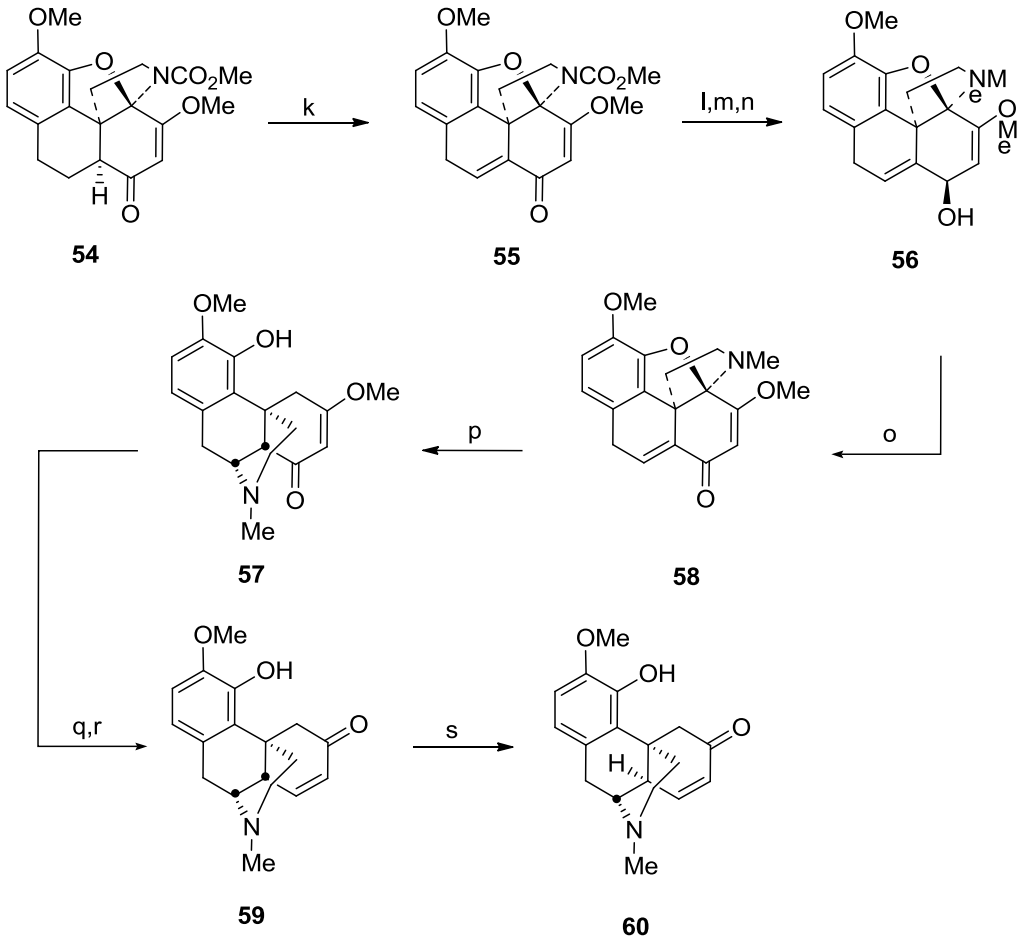
Chloroselenation led to the oxo-bridged adduct **51** from **50**. Deprotection of the keto group, Davis oxidation, and reduction resulted in **53**. The re-aromatized derivative was formed upon Moffat oxidation and was further converted to the **54**.



Reagents and Conditions: a) toluene, 100 ˚C (86%); b) PhSeCl, MeOH; c) H_2O_2, THF (80%); d) aq. HCl, THF; e) KHMDS, THF; f) 3-phenyloxaziradine, THF (82%); g) H_2, Pd/C, THF (75%); h) TFAA, DMSO, NEt_3; i) BF_3•Et_2O; j) CH_3I, K_2CO_3 (56% over three steps).

Scheme 6. Synthesis of intermediate compound **54.**

Further, cleavage of the C-N bond and dihydrofuran rings, N-methylation and re-attachment of the aminoethyl bridge were the key steps to give thebainone-A (**60**).



Reagents and Conditions: k) PhSeCl, EtOAc, then H_2O_2, THF (70%); l) $NaBH_4$, MeOH; m) MeLi, THF; n) HCOH, $NaCNBH_3$, H_2O, CH_3CN (54% over three steps); o) Dess-Martin periodinane, CH_2Cl_2 (75%); p) Zn, NH_4Cl, EtOH, H_2O (73%, 60% conversion); q) DIBAL-H, THF; r) H_3O^+ (quantitative); s) HOAc, 100 ˚C (87%).

Scheme 7. Tius' synthesis of thebainone-A.

Hudlicky (1992, 1995, 1998)[13-15]

In 1992, Hudlicky envisioned that the A and C rings could be constructed from cis-cyclohexenediol and its corresponding catechol which can be obtained from the bio-transformation of aromatic compounds. An adduct of these two pieces could lead to a Diels-Alder reaction to get the phenanthrofuran core of morphinan.

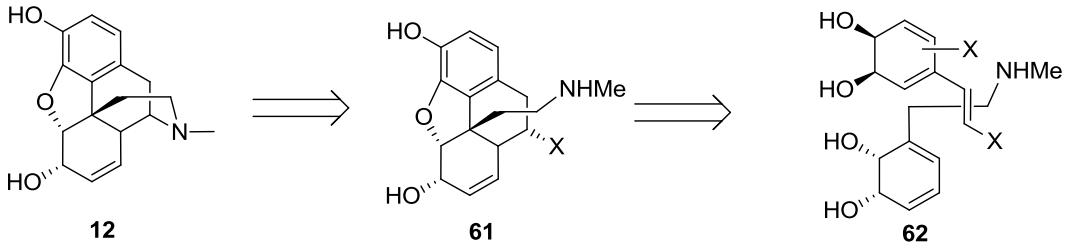
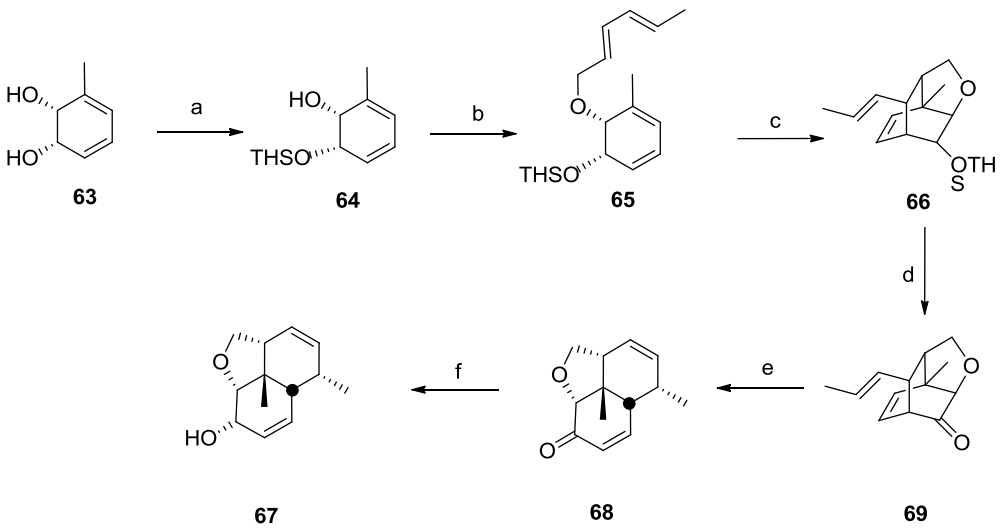


Figure 7. Hudlicky's Diels-Alder strategy.

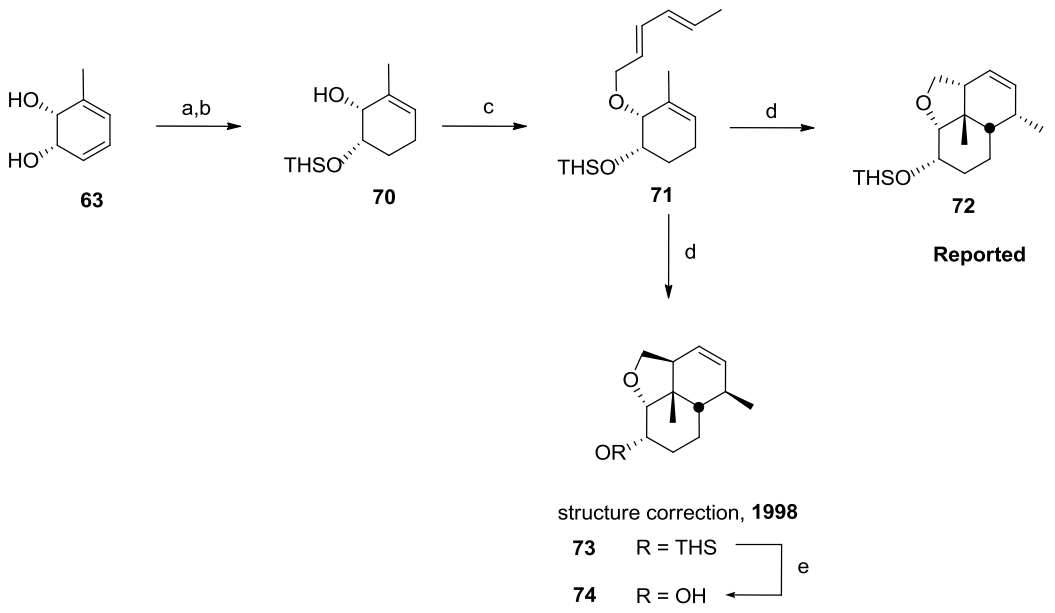
On this basis, model studies were conducted and the key tricyclic core was constructed. One of the alcoholic groups was protected and other one formed an adduct with sorbyl bromide which gave tetraene **65**, where cyclic diene was involved in the cycloaddition reaction. Removal of the silyl protecting group and oxidation of the alcohol to its ketone, then underwent into a tricyclic skeleton via a Cope rearrangement. Luche reduction of the unsaturated ketone gave the allylic alcohol **67** possessing four stereocenters of the morphine skeleton in the correct configuration.



Reagents and Conditions: a) THSCl, imidazole; b) NaH, sorbyl bromide; c) CCl_4, reflux; d) TBAF, then PCC, rt; e) xylenes, 250 ˚C; f) $CeCl_3$, $NaBH_4$, rt.

Scheme 8. Model studies for morphine synthesis.

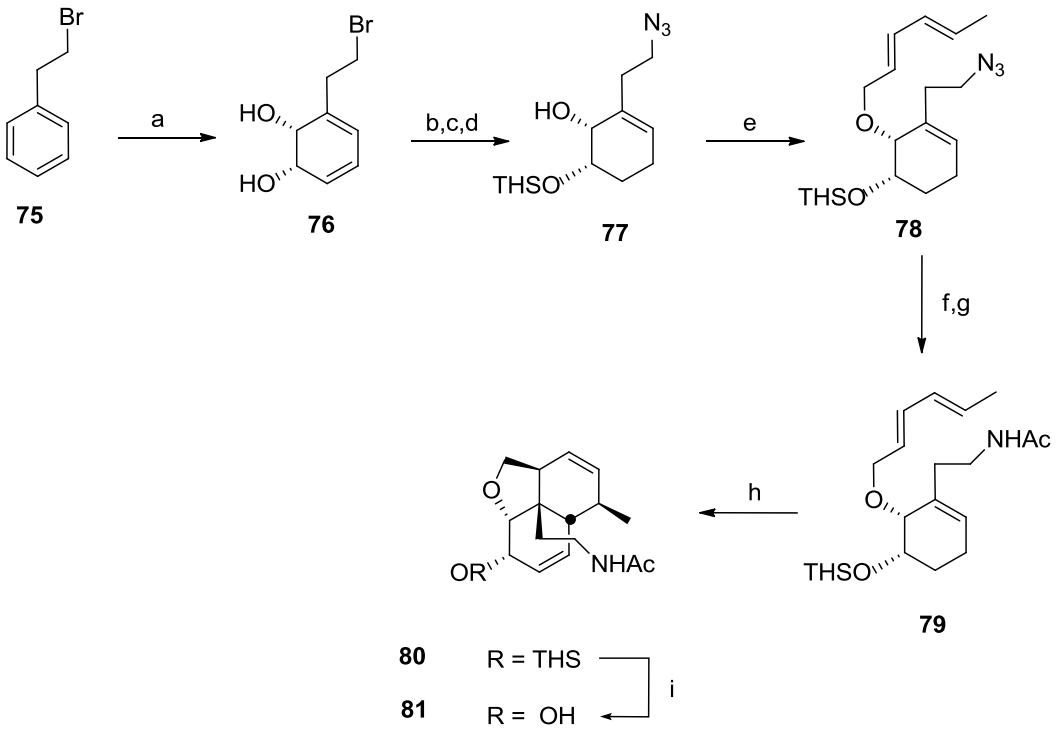
With the second generation model studies the stereochemistry of **67** was proven to be incorrect; it was originally mis-assigned based on nOe correlations. The Diels-Alder adduct indicated that the cycloaddition proceeded via an exo transition state rather than an endo transition state. The less substituted olefin was reduced with the help of a diimide and the less hindered alcohol was selectively protected. *O*-alkylation with sorbyl bromide set the diene part in the molecule and underwent a Diels-Alder reaction to yield the tricyclic core.



Reagents and Conditions: a) PAD, AcOH, MeOH; b) THSCl, imidazole; c) NaH, sorbyl bromide; d) toluene, sealed tube, 210 ˚C; e) TBAF, THF.

Scheme 9. Hudlicky's correction of morphine skeleton structure.

The miss assigned stereochemistry was actually corrected with more sophisticated model studies. Biological oxidation of (2-azidoethyl) benzene readily available from bromoethylbenzene afforded the *cis*-dienediol. The less substituted olefin was reduced with diimide and the less hindered alcohol was selectively protected. Alkylation of the allylic oxygen and **71** formation set the triene for a Diels-Alder reaction. X-ray crystallographic analysis confirmed the stereochemistry of the [4+2] cycloaddition, preceded via an *exo* transition state. This result helped to reinvestigate the formal structural correction of cycloadduct **72**, giving a very direct route to construct the morphine skeleton with the correct stereochemistry.

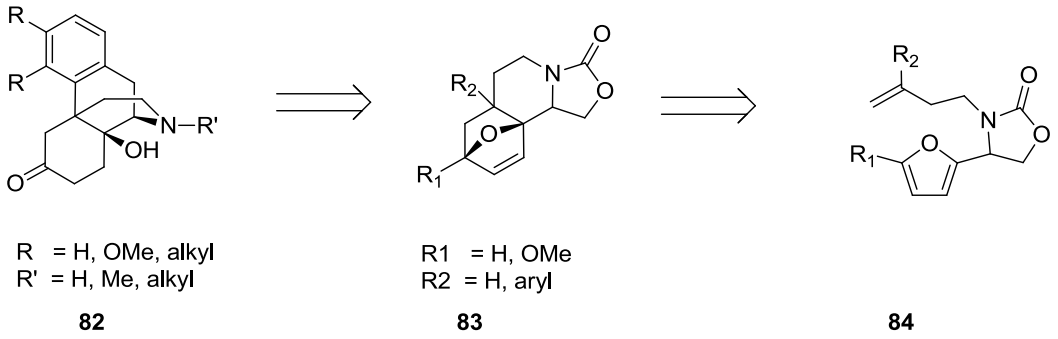


75 76 77 78 79

Reagents and Conditions: (a) *E. coli* JM109 (pDTG601), (10 g/L); (b) NaN_3, DMF; (c) potassium azodicarboxylate (PAD), AcOH, MeOH (72%); (d) THS-Cl, imidazole, DMF (99%); (e) NaH, sorbyl bromide, THF (62%); (f) Ph_3P, H_2O (66%); (g) Ac_2O, py (quantitative); (h) toluene, sealed tube, 230 ˚C (62%); (i) 45% aq HF, MeCN (65%).

Scheme 10. Hudlicky's strategy for the B, C, D ring system synthesis of morphine.

Later, in 1995 the Hudlicky group visualized that the heteroaromatic ring could act as a diene for Diels-Alder reaction and would be helpful for the construction of isoquinoline morphine synthons.



R = H, OMe, alkyl
R' = H, Me, alkyl

82

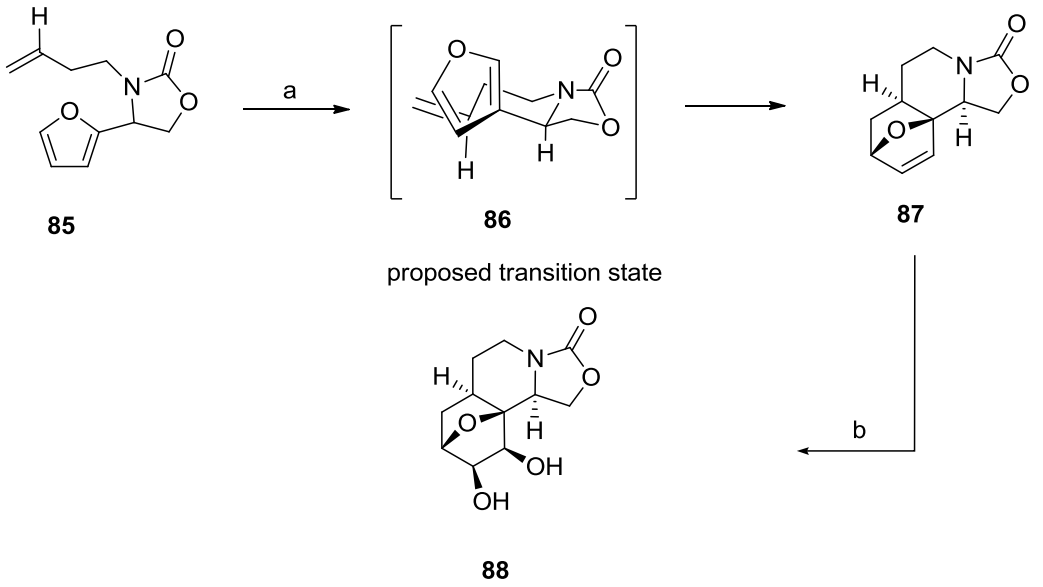
R1 = H, OMe
R2 = H, aryl

83

84

Figure 8. Hudlicky's approach for isoquinoline morphine synthons.

With this vision, model studies had been conducted. In the Scheme 11 oxazolidinone **85** underwent thermal Diels-Alder cyclizations in two ways: first by simple heating in toluene at 200 ˚C with a 56% yield; and second, by heating at much lower temperature (65-90 ˚C) in the presence of *β*-cyclodextrin with an 84% yield. The stereochemistry of the model tricycle was proven by single-crystal X-ray analysis. Hudlicky postulated that the transition state has a chair-like conformation in which the furan adopted an *exo*-position.

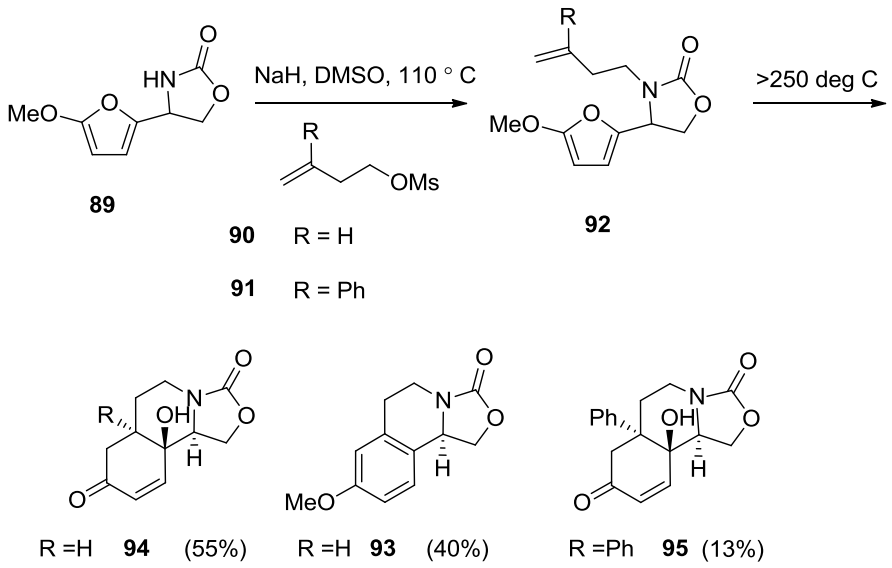


85 **86** **87** **88**

Reagents and Conditions: a) 90 ˚C, cyclodextrin (84%); b) OsO_4, *t*-BuOH-H_2O (95%).

Scheme 11. Proposed transition state postulated for model isoquinoline cyclizations.

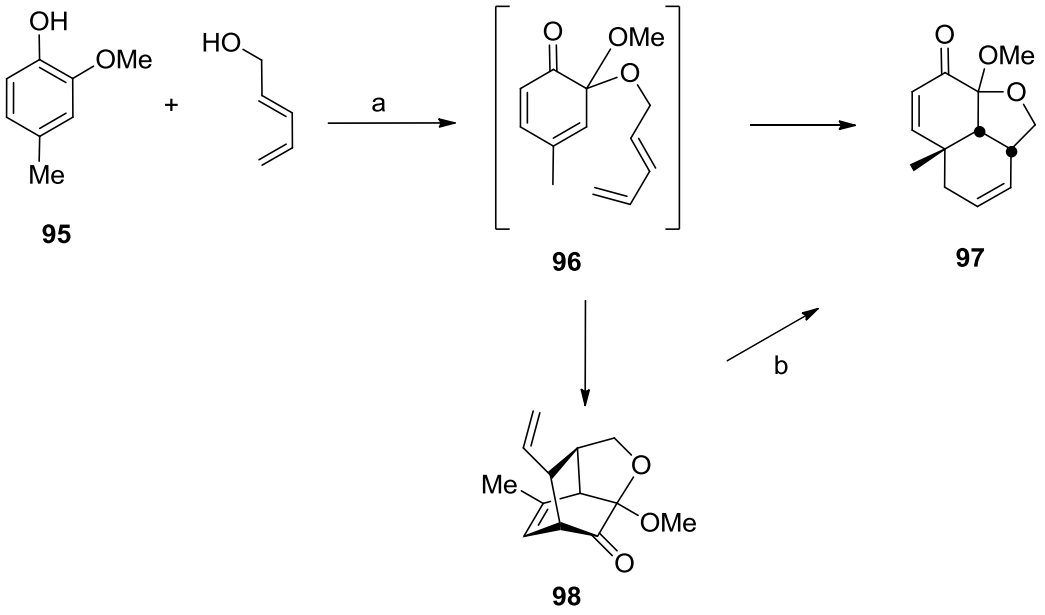
With this preliminary result, subsequent model studies examined the 2-methoxyfuran derivatives were studied. When R = H, the anisole **93** (40%) and the enone **94** (55%) were formed upon thermal cyclization but in the case of R= Ph the Diels-Alder reaction gave the advanced isoquinoline derivative **95** with a 13% yield. These studies showed that morphine synthons could be constructed by the intramolecular Diels-Alder reaction of furans.



Scheme 12. Morphine synthons

Rodrigo (1998)[16]

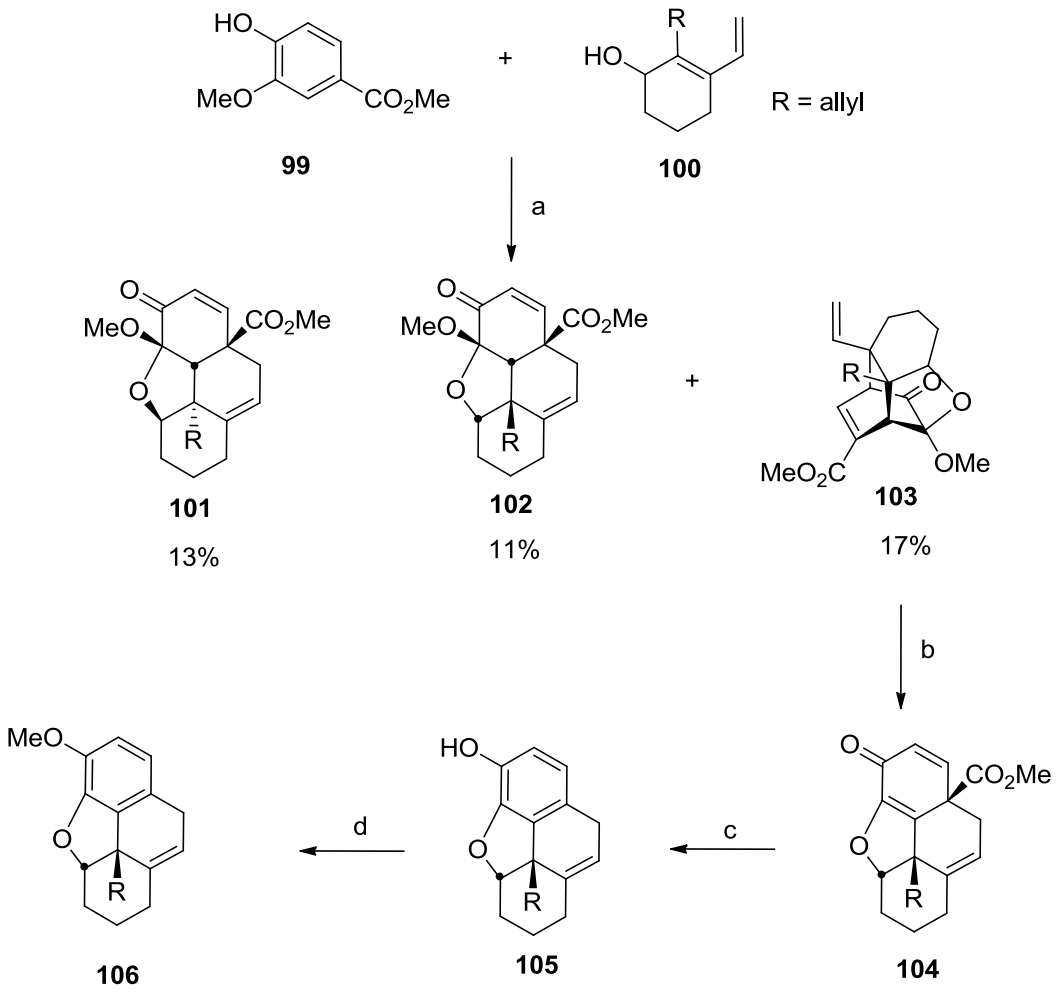
Rodrigo recognized that *o*-substituted phenolic ethers undergo oxidative coupling with alcohols to give mixed ketals. With this strategy, he synthesized ketals that contained diene and dinophile parts in a single molecule. This ketal readily underwent an intramolecular Diels-Alder reaction without isolation of the ketal adduct intermediate. Two possible Diels-Alder adducts were formed in the process, one with the desired stereochemistry which could be extended to form the morphine skeleton while the other rearranged to give **97**.



Reagents and Conditions: a) BTIB, THF ; b) [3,3]-sigmatropic rearrangement.

Scheme 13. Rodrigo strategy to construct morphine skeleton.

With this success, Rodrigo used the same strategy to make the A, B and C rings of morphine skeleton. Rodrigo synthesised the desired in situ ketal adduct from vanillate and allylic alcohol which underwent spontaneously into three possible Diels-Alder products. Desired Diels-Alder adduct **102** (11%) was formed while diastereomers **101** with (13%) and the bridged bicycle **103** with (17%) yield. Thermal Cope rearrangement of **103** gave the tetracycle **104**, which underwent rearomatization to **105** losing the methyl ester group. Phenol was methylated to give the phenanthrofuran skeleton **106**.



Reagents and Conditions: a) BTIB, THF; b) DME, reflux (59%); c) NaOH, MeOH (94%); d) K_2CO_3, Me_2SO_4 (75%).

Scheme 14. Rodrigo's Diels-Alder/Cope approach to phenanthrofurans.

Stork (2009)[17]

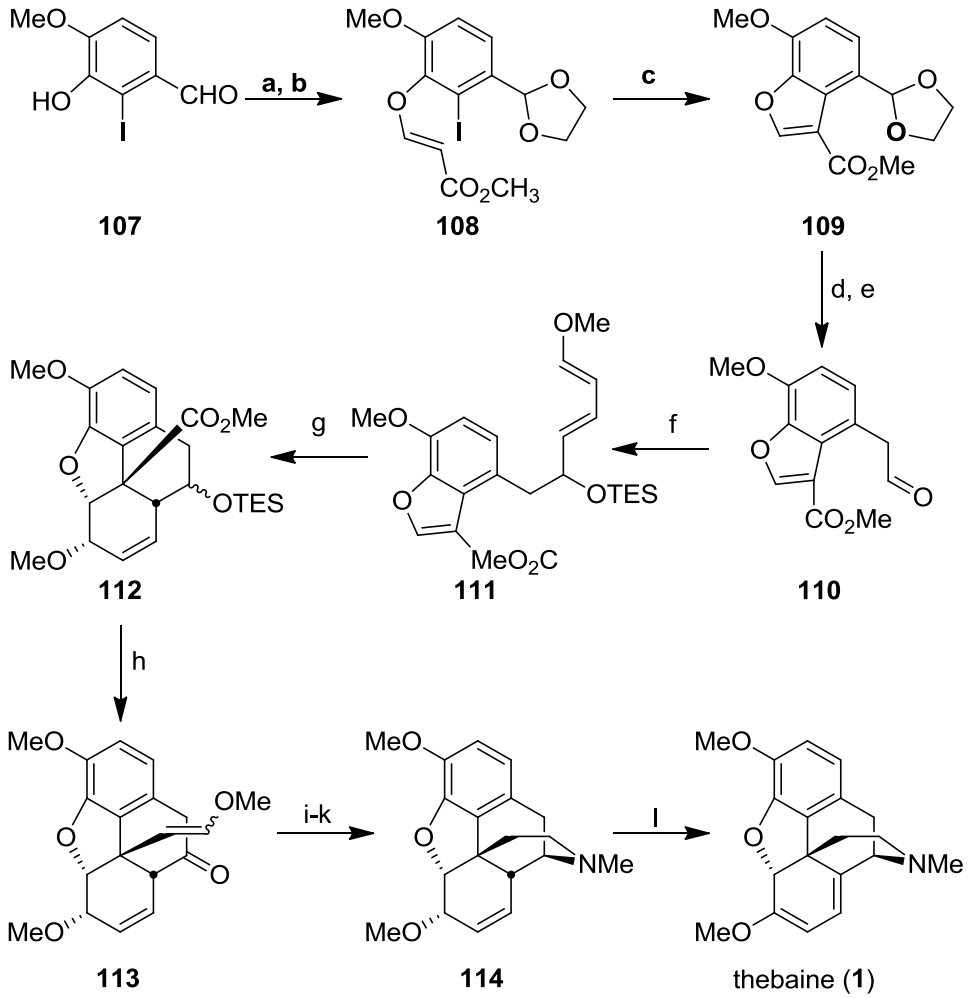
Stork's strategy for the synthesis of morphine alkaloids via a highly stereocontrolled intramolecular 4 + 2 cycloaddition to establish the B- and C-ring of the morphine alkaloid.

The Diels-Alder precursor was prepared in 6 steps from iodoisovanillin which was converted to **151** in two steps. An intramolecular Heck coupling gave **152**, removal of the keto group and extention of the aldehyde through a Wittig

reaction give **153** which was converted into the Diels-Alder precursor through homologation of the aldehyde.

Then it was heated in decalin at 240 ˚C in a sealed pressure flask, in the presence of triethylamine to result in the desired cycloaddtion reaction. Cleavage of the protecting silyl ether group, oxidation to a keto group, and conversion of the methyl ester to its enol ether gave **156**. The C-9 ketone was reduced and converted to its mesylate prior to introduction of the methylamine via a reductive amination. The resulting methylamine group displaced the mesylate to give the cyclised product (+) codeine methyl ether (**157**). **157** is a know intermediate of Rappoport's synthesis of thebaine.[18]

Important features of the Stork's synthesis were to set the correct relative stereochemistry of the five contiguous asymmetric carbon atoms in a single step reaction and only a minor diastereoisomer was formed.



107 108 109 110 111 112 113 114

Reagents and Conditions: (a) $HO(CH_2)_2OH$, *p*-TsOH, toluene (85%); (b) methyl propiolate, Et_3N, THF (89%); (c) $Pd(OAc)_2$, Ph_3P, NaOAc, n-Bu_4NCl, DMF, 125 °C (84%); (d) HCl, THF (98%); (e) (i) $Ph_3PCH_2OCH_3Cl$, KHMDS, THF, (ii) HCl, THF (95%); (f) (i) 4-methoxy-3-butene-1-yne, $ZrCp_2(H)Cl$, AgOTf, CH_2Cl_2, (ii) TESCl, imidazole (95%); (g) Decalin, Et_3N, 240 °C, 24 h (69%); (h) (i) Super hydride, THF, (ii) Dess-Martin, CH_2Cl_2, (iii) $Ph_3PCH_2OCH_3Cl$, KHMDS, CH_2Cl_2-THF, (iv)TBAF, THF, (v) Dess-Martin, CH_2Cl_2, 0 °C (51%); (i) L-Selectride, THF, 0 °C, (ii) MsCl, Et_3N, CH_2Cl_2, 0 °C

(34%); (j) (i) HCl, THF, (ii) $MeNH_2 \cdot HCl$, Et_3N, $Ti(OiPr)_4$, MeOH, (iii) $NaBH_4$ (80%); (k) K_2CO_3, benzene, 75° C, 24 h; (l) Reference 18.

Scheme 15. Stork's synthesis of thebaine.

II-3 Pyridazine

II-3.1 Use in synthetic chemistry

The reactivity differences of benzene and pyridine are well-known as compared to those of benzene and pyridazine. Some of the general features of pyridazine chemistry can be summarized as follows.

Reactions with Electrophilic Reagents:

Pyridazines are electron-deficient heterocycles and are generally resistant to electrophilic substitution on the pyridazine ring. The reason being, the aromaticity of pyridazine is distorted because of electrophilic substitution at one of the carbon centers of the ring, which is further deactivated by two electronegative nitrogens. Therefore, the electrophilic addition is more favoured at nitrogen.

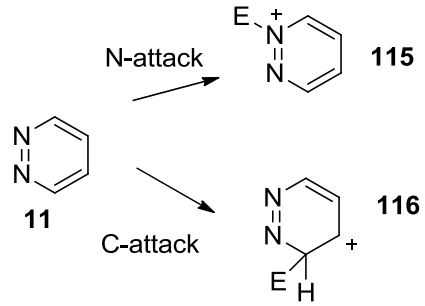


Figure 9. Electrophilic substitution with pyridazine.

Alkylation:

Pyridazines reacts with activated alkyl halides through S_N2 displacement to give the mono-quaternary salts. Additionally, unsymmetrically substituted pyridazines can give rise to two isomeric quaternary salts. Substituents influence the orientation mainly by steric and inductive effects, rather than mesomeric effects. For example, 3-methylpyridazine alkylates mainly at N-1, even though N-2 is the more electron-rich site. Yet another example is quaternisation of 3-methoxy-6-methylpyridazine which takes place adjacent to the methyl substituent, at N-1, although mesomeric release would have been expected to favour attack at another nitrogen atom.[19]

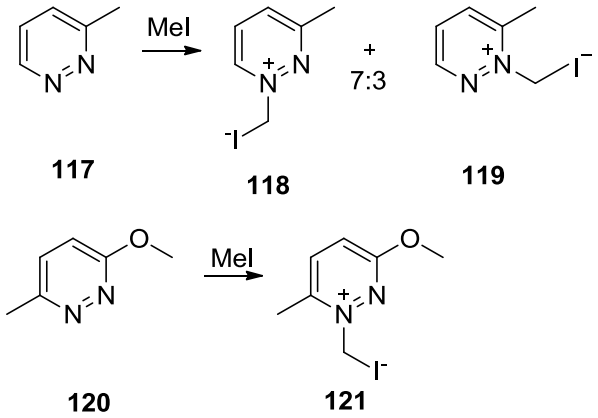


Figure 10. Alkylation of pyridazine.

Oxidation:

Pyridazines react with peracids to form N-monoxides. Intrestingly, the regiochemistry of N-oxidation is the same as N-alkylation. For example, 3-aminopyridazine gives mainly 2-oxides, but 3-methylpyridazine provides the 1-oxide as the main (3:1) product (figure 11).[20]

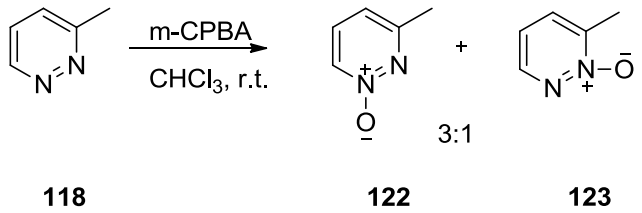


Figure 11. Oxidation of pyridazine.

Electrophilic Subsitution at Carbon:

The aromatic electrophilic substitution reaction is difficult to attain at the ring's C- atoms as a result of the electron withdrawing nature of the N atom. Electrophilic substitution of pyridazine, mainly takes place in the presence of electron-donating substituents.[21] It is worth noting that N-oxidation facilitates the substitution in some of the cases.[22]

4-Amino-3,6-dimethoxypyridazine undergoes nitration to afford the 5-nitro compound. However, the less highly activated 3-methoxy-5-methylpyridazine requires more vigorous conditions to yield a complex mixture of 4-nitro, 6-nitro, and 4,6-dinitro derivatives. Pyridazine 1-oxide and many of its substituted derivatives undergo nitration with nitric and sulfuric acid to form the corresponding 4-nitropyridazine-1-oxide **125** (figure 12)[21]:

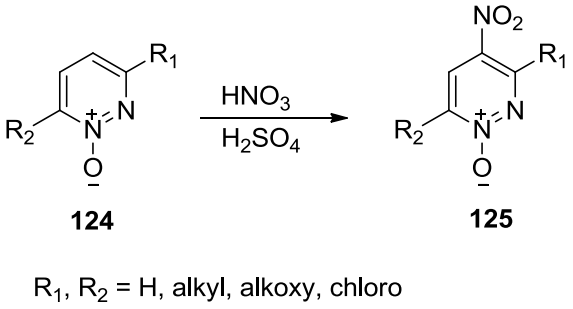
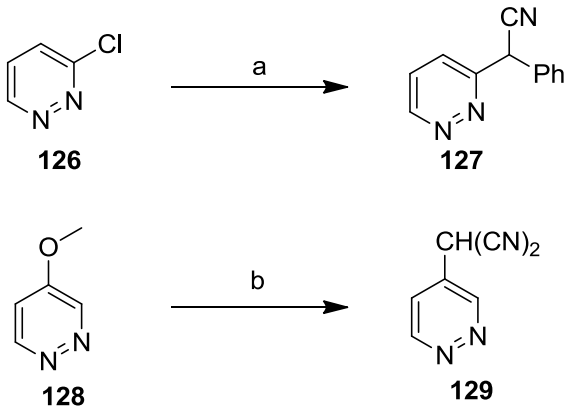


Figure 12. Electrophilic substitution reactions at carbon of pyridazine.

Reactions with Nucleophilic Reagents:

The pyridazines are reactive towards nucleophilic addition due to the presence of nitrogen atoms. The nucleophilic substitution goes smoothly with good leaving groups. For example, halopyridazine react with nucleophiles with a halide ion as a leaving group. In addition, nucleophiles can also displace methoxy groups via an addition/elimination process.[23]

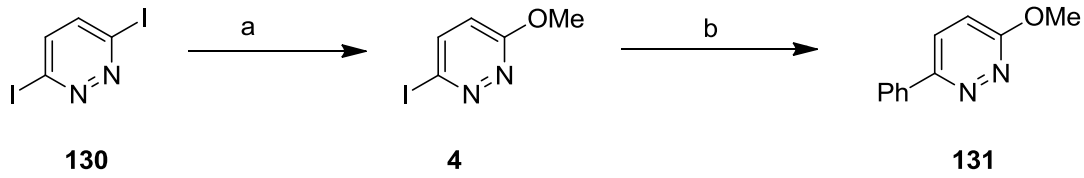


126 **127** **128** **129**

Reagents and Conditions: (a) $PhCH_2CN$, $NaNH_2$, PhH, reflux (65%); (b) $CH_2(CN)_2$/NaH, dioxane, reflux (62%).

Scheme 16. Nucleophic substitution of pyridazine.

Unsymmmetrically disubstituted pyridazines can also be prepared in a stepwise manner. For example, nucleophilic mono-substitution is followed by a palladium-catalyzed coupling with an arylboronic acid.[24]



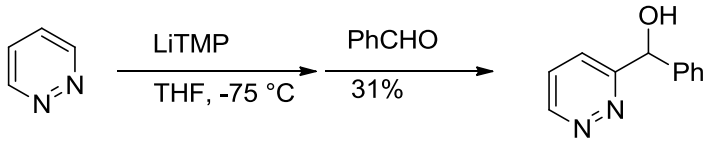
130 **4** **131**

Reagents and Conditions: (a) NaOMe/MeOH, reflux, 12 h (92%); (b) $PhB(OH)_2$, $Pd(PPh_3)_4$, Na_2CO_3, PhMe (76%).

Scheme 17. Synthesis of unsymmmetrically disubstituted pyridazine.

C-H activation reactions of pyridazine:

Pyridazines are usually difficult to ortho-metalate because of the low LUMO energy, which makes them reactive towards nucleophile additions. Because of this reason, non-nucleophilic lithium 2,2,6,6-tetramethylpiperidide (LiTMP) is a more efficient ortho-metalating agent than the alkyllithiums. However, the heteroaryllithium species are very unstable and can easily dimerize. These conditions could be avoided by using very short lithiation time or by in-situ trapping with compatible electrophiles.[25]

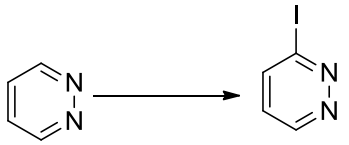


11 **132**

Figure 13. C-H activation from LiTMP.

Generally, the lithiation requires low temperature reactions. In 2007, Florence Mongin and co-workers reported mild condition to do ortho substitution of pyridazine using a zinc diamide-lithium amide mixture. Deprotonation of

pyridazine with $ZnCl_2$.TMEDA and LiTMP trapped with iodine result in a good yield of 3-iodopyridazine in THF at reflux.[26]

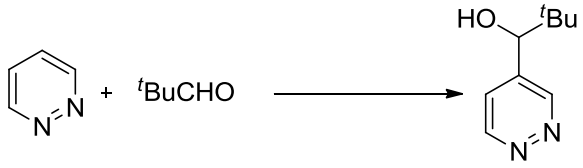


11 **133**

Reagents and Conditions: $ZnCl_2$.TMEDA, and LiTMP, THF, 0 °C to reflux, (66%).

Scheme 18. Ortho-substitution of pyridazine using a zinc diamide-lithium amide mixture.

In 2003 Kondo reported that the direct zincation of pyridazine occurs at position 4 instead of position 3 when using a hindered phosphazene *t*-BuP_4 base and zinc (II) iodide as an additive in toluene.[27]

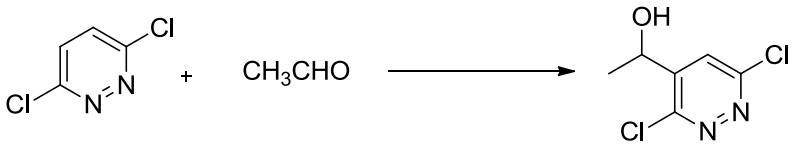


11 **134** **135**

Reagents and Conditions: ZnI_2, *t*-Bu-P_4, PhMe, -78 °C to rt (73%).

Scheme 19. Zincation of pyridazine.

Lithiation of pyridazine with a directing group is an easy and a high yielding process.[28]



5 **136** **137**

Reagents and Conditions: LiTMP, -70 °C, then **136** (65%).

Scheme 20. Pyridazine with a directing group.

Ortho-lithiation of pyridazine with chiral molecules like chiral sulfinate esters has been reported by Queguiner and coworkers.[29] The resulting chiral sulfoxides can be subjected to a second ortho-lithiation with different aldehydes to provide fully-substituted pyridazines with high diastereoselectivities.

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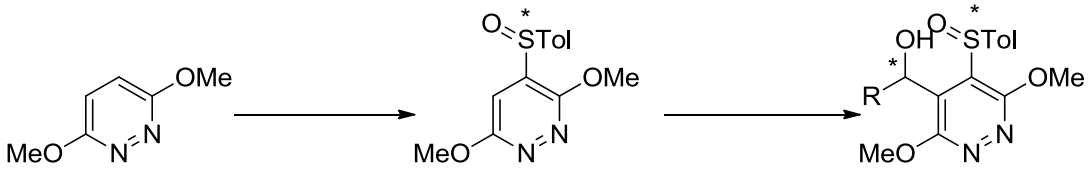


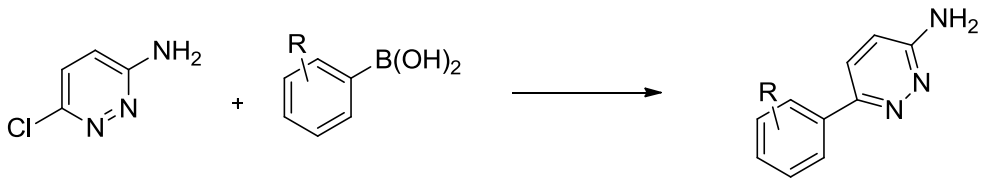
138 **139** **140**

Reagents and Conditions: a) LTMP, (S) or (R)-menthyl *p*-toluenesulfinate (76-77%); b) LTMP or LDA, RCHO, (76-80%).

Scheme 21. Ortho-lithiation of pyridazine with chiral molecules.

Coupling Reactions:

Rival and co-workers reported the first Suzuki cross-coupling of pyridazine with palladium-mediated chemistry. Electron-donating substituents on the arylboronic acid provided optimal yields.[30]

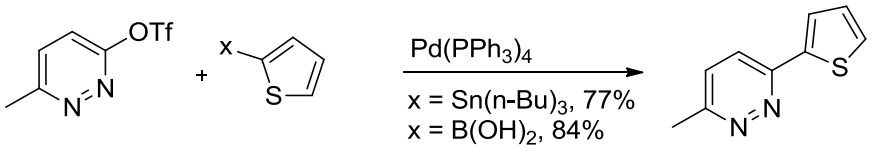


141 **142** **143**

Reagents and Conditions: $Pd(PPh_3)_4$, Na_2CO_3, 30-60%

Scheme 22. Cross-coupling of pyridazine.

Similar studies on palladium-catalyzed Stille and Suzuki coupling reactions of pyridazinyl triflates have been reported by Aldous and co-workers with electron-rich arylstannanes and aryl boronates. In general, the Suzuki reaction was found to be more efficient than the corresponding Stille cross-coupling reaction.[31]

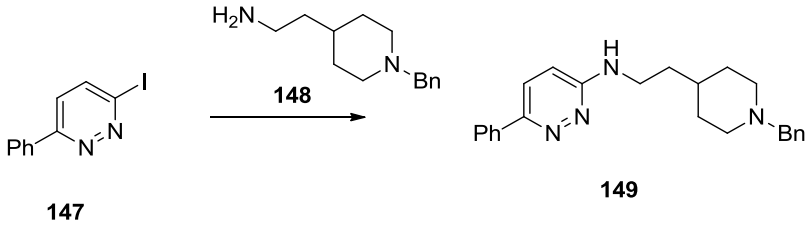


144 **145** **146**

Figure 14. Stille and Suzuki coupling reactions of pyridazine.

Direct amination of 3-chloropyridazines with primary amines usually needs harsh conditions and results in poor yielding reactions. It was found that palladium cross-coupling reactions form a smooth carbon–nitrogen bond. Hibert[32]

reported a palladium-assisted procedure for the amination of 3-iodo-6-arylpyridazines **147**.



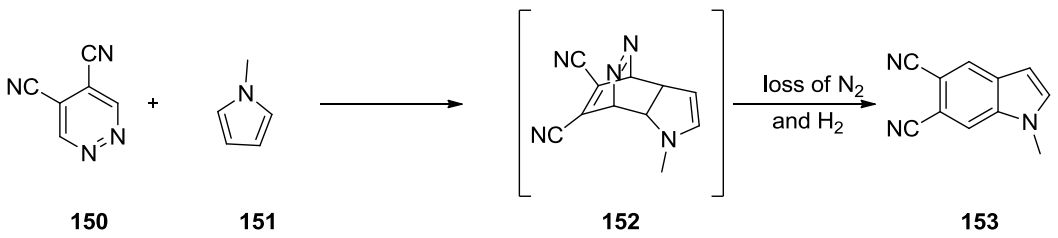
Reagents and Conditions: $PdCl_2$(dppf), dppf, *t*-BuONa, 80 °C, 6h (75%).

Scheme 23. Amination of compound **147**.

II-3.2 Use of pyridazine in Diels-Alder reaction

The Diels–Alder cycloadditions of pyridazines have proven to be valuable. The reaction is very fundamental for the construction of key intermediate compounds for the synthesis of various natural products. Pyridazine rings generally undergo inverse electron-demand Diels-Alder reactions due to deficient properties of π electrons. The presence of electron withdrawing substituents on pyridazine ring enhances their reactivity towards electron-rich dienophiles. Electron withdrawing substituents lead to a decrease in its LUMO energy and favours inverse Diels-Alder reactions. The immediate products of such processes usually lose nitrogen for subsequent retro-Diels–Alder reaction.

Pyridazines give low to moderate yielded cycloadduct products for intermolecular hetero Diels-Alder reactions. For example, 4,5-dicyanopyridazine with N-methylpyrrole reacts at 150 °C to give a Diels–Alder adduct and subsequent loss of H_2 and N_2 provide indole heterocycles.[33]

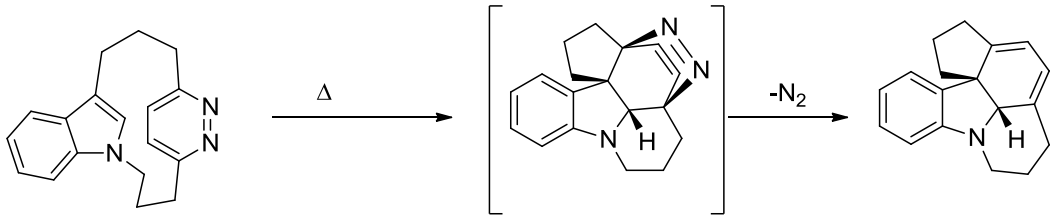


150 151 152 153

Reagents and Conditions: Xylene, 150 °C (55%).

Scheme 24. Intermolecular hetero Diels-Alder reactions example.

Intramolecular Diels–Alder reactions of pyridazines work well with doubly tethered pyridazine. For example, cyclophane was heated in N,N-diethylaniline and led to the formation of pentacyclic product **156** in quantitative yield while the same reaction in mesitylene gave a yield of 21%.[34]

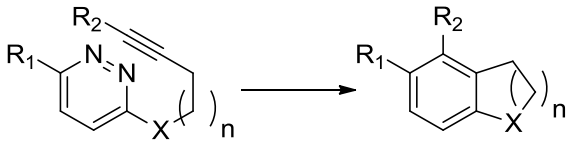


154 155 156

Reagents and Conditions: Mesitylene, 10 d, 21% or *N*, *N*-diethylaniline, 2d (90%).

Scheme 25. Intramolecular Diels–Alder reactions of pyridazines.

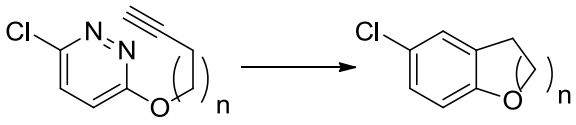
In 1983 Boger investigated the effects of the length of the alkyne side chain (*n* = 1,2,3), substitution (R_1 = H, C1; R_2 = H, CH_3, CH_2OR), and heteroatom (X = O, NCO_2CH_3) on the intramolecular thermal cycloaddition of pyridazine.[35]



157 158

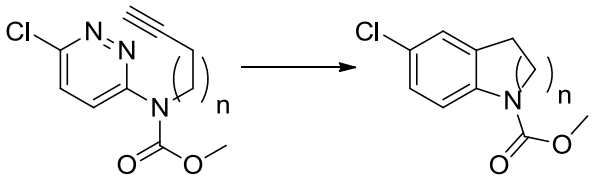
Figure 15. Investigation of the intramolecular cycloaddition of pyridazine.

The result of the study suggested that the variation in the length of the alkyne side chain (*n* = 1) and heteroatom (X= NCO_2CH_3) mainly affected the outcome of intramolecular Diels-Alder reaction of the alkyne 1,2-diazines.



159 160

n = 1, trace
n = 2, 0%
n = 3,0%



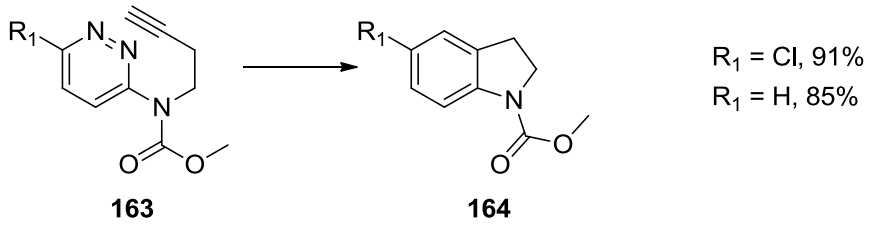
161 162

n = 1, 84%
n = 2, 0%
n = 3,0%

Reagents and Conditions: 1,3,5-triiipropylbezene, 150-250 °C, 6-24 h.

Scheme 26. Effect of alkyne side chain and heteroatom on the Diels-Alder reaction.

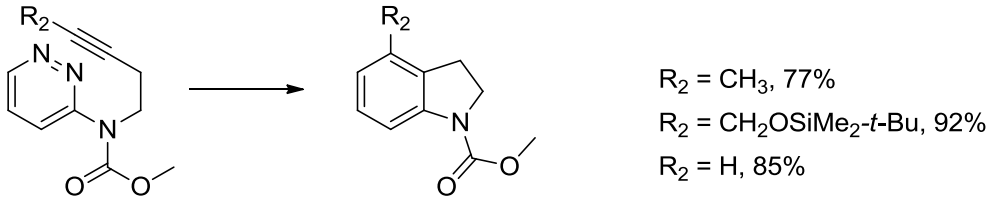
The substitution of R_1 and R_2 hardly have any effect on the rate of cycloaddition.



163 **164**

Reagents and Conditions: 1,3,5-triiipropylbezene, 230 °C, 12 h.

Scheme 27. Effect of subsitution of the pyridazine ring on the Diels-Alder reaction.



165 **166**

Reagents and Conditions: 1,3,5-triisopropylbenzene, 230 °C, 18h.

Scheme 28. Effect of subsitution of alkyne side chain on Diels-Alder reaction.

II-4 Previous approaches in the Hudlicky group towards the synthesis of thebaine

The synthesis of thebaine is based on the latent pseudo-symmetry that is present in the thebaine molecule. Based on this symmetry, it is visualized that the thebaine core could be constructed through a cascade of sulfoxidation/ intramolecular Diels-Alder reactions of compound **167** (figure 16).

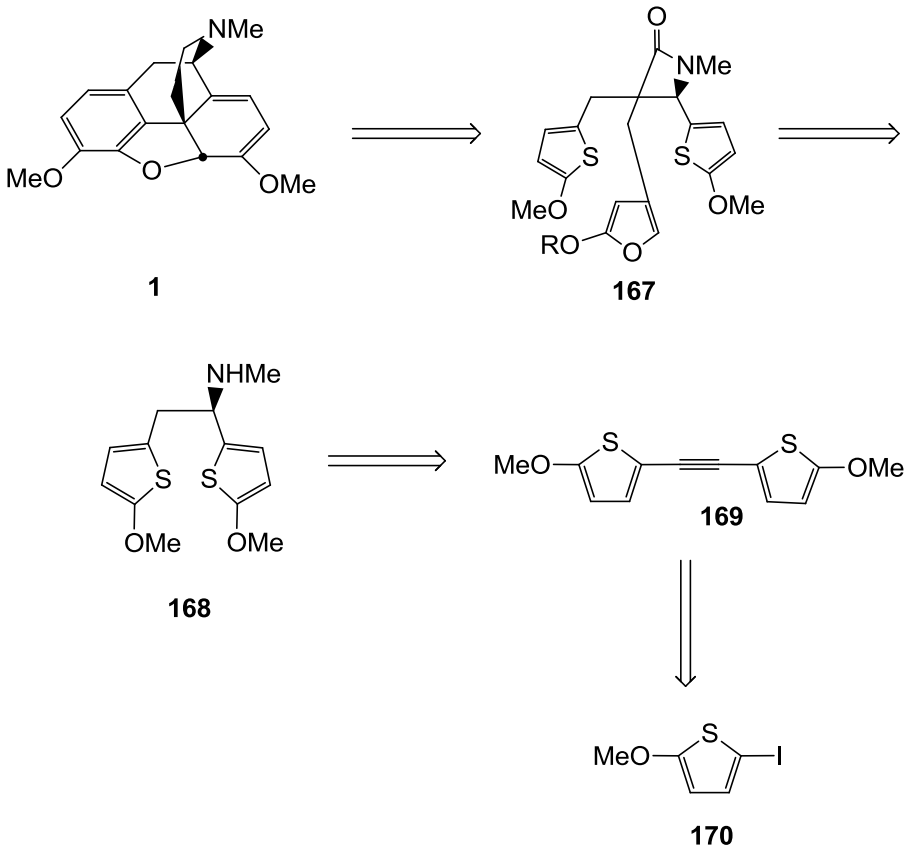
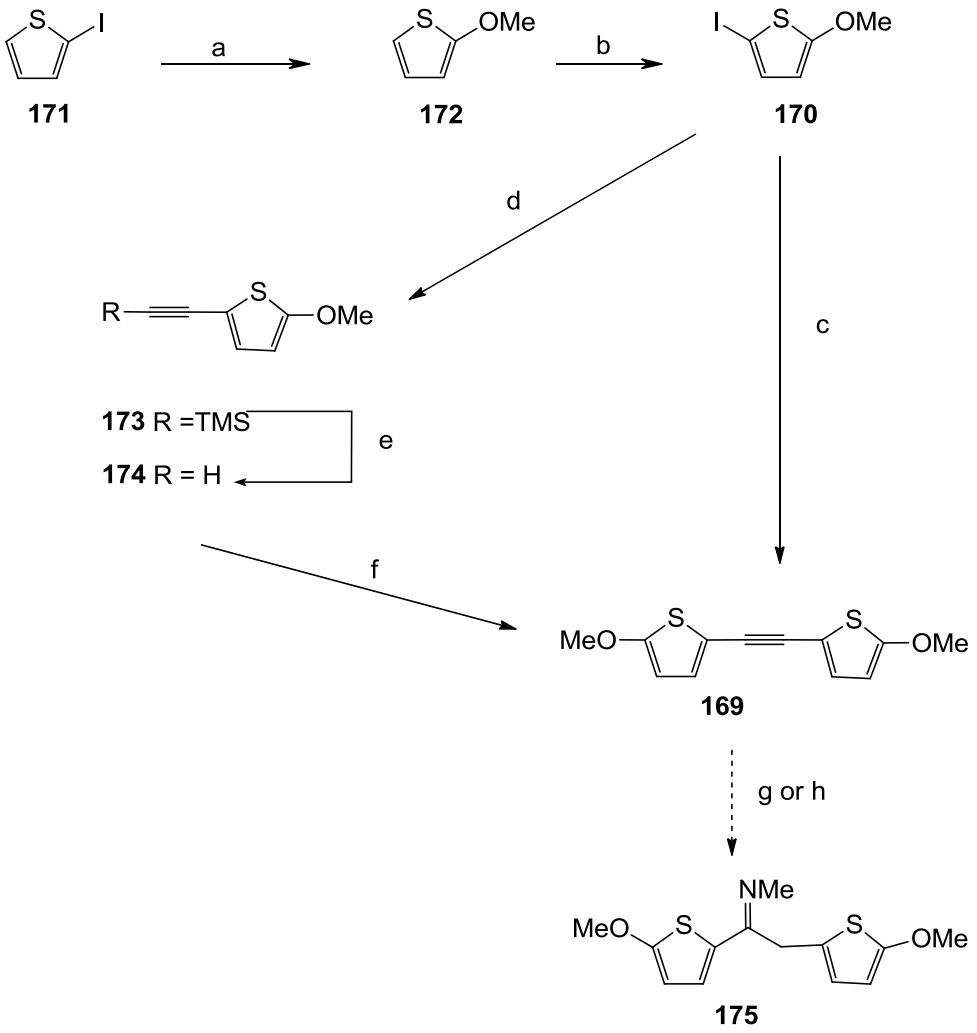


Figure 16. The retrosynthetic analysis of thebaine using thiophene as a masked diene.

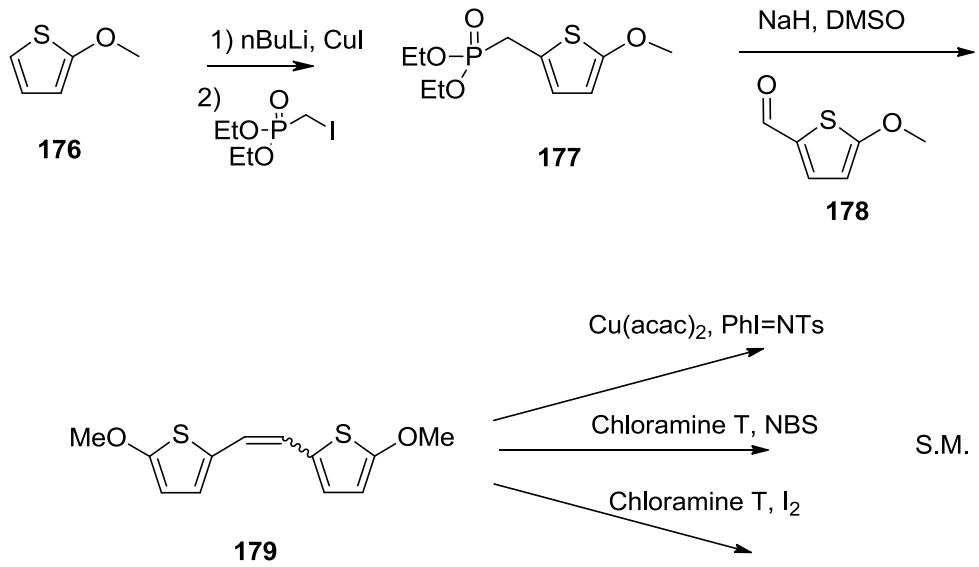
With this strategy, Dr. Kevin Finn[36] used 2-iodothiophene as a starting material. 2-Iodothiophene was converted to 2-methoxythiophene and then into 2-Iodo-5-methoxythiophene. This iodo derivative was converted into compound **169** in a single step or in a stepwise manner through a Sonogashira reaction. This alkyne **169** was subjected to hydroamination conditions but **169** never gave the desired hydroamination product **175** and only the starting material was recovered.



Reagents and Conditions: a) NaOMe, MeOH, CuO (76%); b) I_2, HgO, benzene, CH_2Cl_2 (76%), c) TMS-acetylene, $Pd(PPh_3)_4$, TEBAC, CuI, benzene, 2.5 N aq NaOH , sealed tube (32%) ; d) TMS-acetylene, $Pd(PPh_3)_2Cl_2$, $^{i}Pr_2NH$, CuI; e) TBAF, THF, rt (65%); f) $Pd(PPh_3)_2Cl_2$, NEt_3, CuI, **171**, (36%); g) toluene, 1M $MeNH_2$ in THF, 120 °C, seal tube; h) toluene, $MeNH_2$, $IndTiMe_2$, 120 °C.

Scheme 29. Thiophene strategy for the synthesis of thebaine.

Alternatively, a corresponding alkene of compound **169** was synthesized and subjected to a variety of aziridination conditions without any success (Scheme 30).



Scheme 30.

At this point model studies had been done to assess the feasibility of the tandem oxidation/Diels-Alder sequence. Retro synthetic analysis of model studies are shown in figure 17 as below:

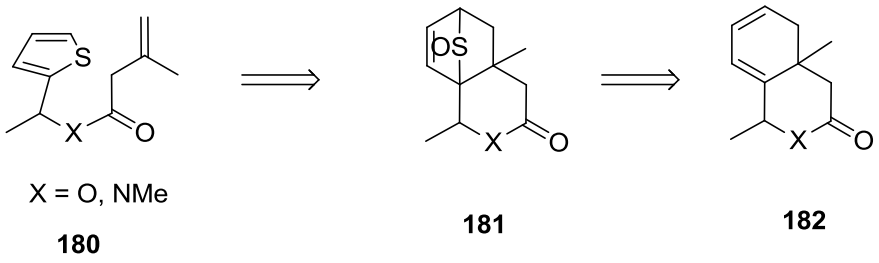
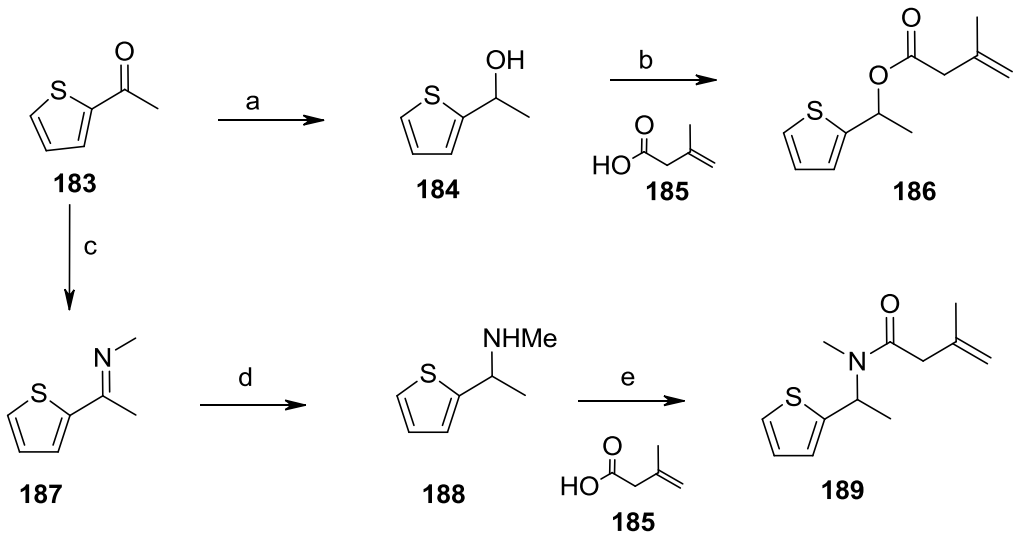


Figure 17. Retro synthetic analysis of thiophene based model.

Commercially available 2-acetyl thiophene was used as a starting material and converted into compound **186** in two steps. An analogous amide of compound

189 was also prepared from 2-acetyl thiophene in two steps in order to determine the feasibility of the tandem oxidation/Diels-Alder sequence.

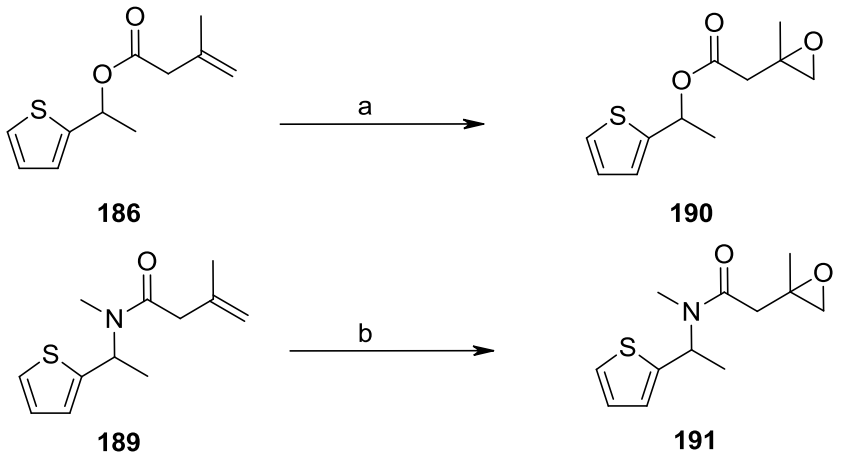


Scheme 31. Thiophene-based model compound synthesis route.

Reagents and Conditions: a) $NaBH_4$, MeOH; b) DMAP, DCC, DCM (33%), c) methylamine, *p*TsOH, toluene, quant.; d) $NaBH_4$, MeOH (68%); e) DMAP, DCC, DCM (39%).

Compounds **186** and **189** were subjected to an enzymatic oxidation by *Escherichia coli* JM 109 pDTG061. Ester **186** gave a hydrolysis product and the amide **189** was found to be resistant to enzymatic oxidation.

Later, the known chemical oxidation condition for thiophene was also investigated but only the starting material or decomposed product were observed for **186** and **189**. Furthermore, an oxidation using *m*CPBA gave the epoxy product as shown in Scheme 32.

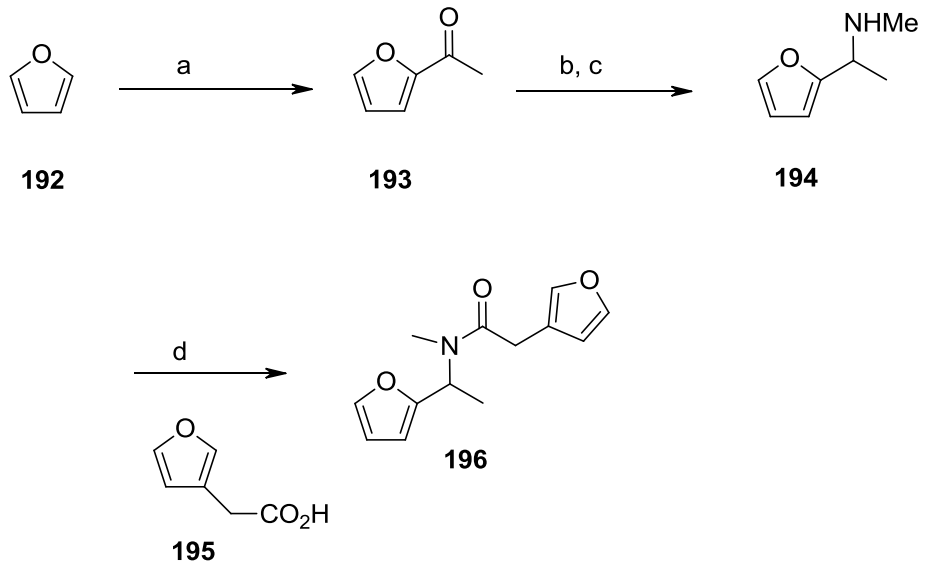


Scheme 32. Epoxy products.

Reagents and Conditions: a) *m*CPBA, DCM (62%); b) *m*CPBA, DCM (70%).

At this point, furan based model studies had also been investigated in which a furan would serve as a latent diene for an intramolecular furan Diels-Alder reaction.

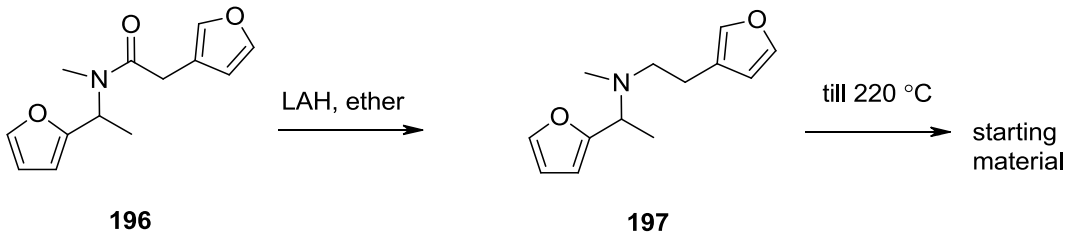
Furan was used as a starting material. Furan was acylated to get 2-acetylfuran, then converted into compound **194** and this amine was coupled with an acid **195** to get amide **196** as shown in Scheme 33.



Scheme 33. Furan based model compound.

Reagents and Conditions: a) BF_3OEt, $(Ac)_2O$; b) NH_2Me, $TiCl_4$; c) $NaBH_4$, *i*PrOH (56% in 2 steps); d) DMAP, EDC, DCM (87%).

The amide **196** was subjected to various Diels-Alder reaction. $Sc(OTf)_3$ and $Yb(OTF)_3$ were found to be an ineffective catalysts, while $AlCl_3$ and $TiCl_4$ resulted in the destruction of the starting material. Furthermore, **196** was stable for thermal (greater than 200 °C) Diels-Alder reaction. Compound **196** was reduced to corresponding **197** and was also found to be stable for thermal Diels-Alder reaction.



Scheme 34. Thermal Diels-Alder reaction attempt.

Later pyridazine was chosen by Dr. Jon Collins[37] to investigate the validity of intramolecular Diels Alder reactions. It was observed that two suitably substituted pyridazines and the appropriate furan-based dieneophile could undergo intramolecular Diels-Alder reactions as shown in figure 18.

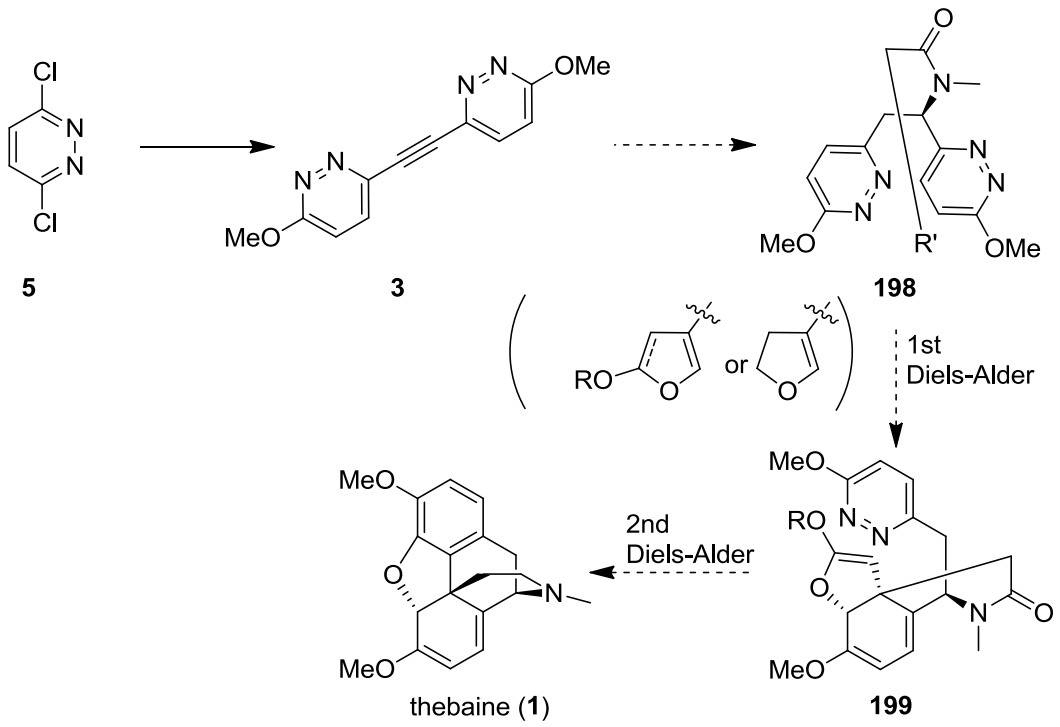
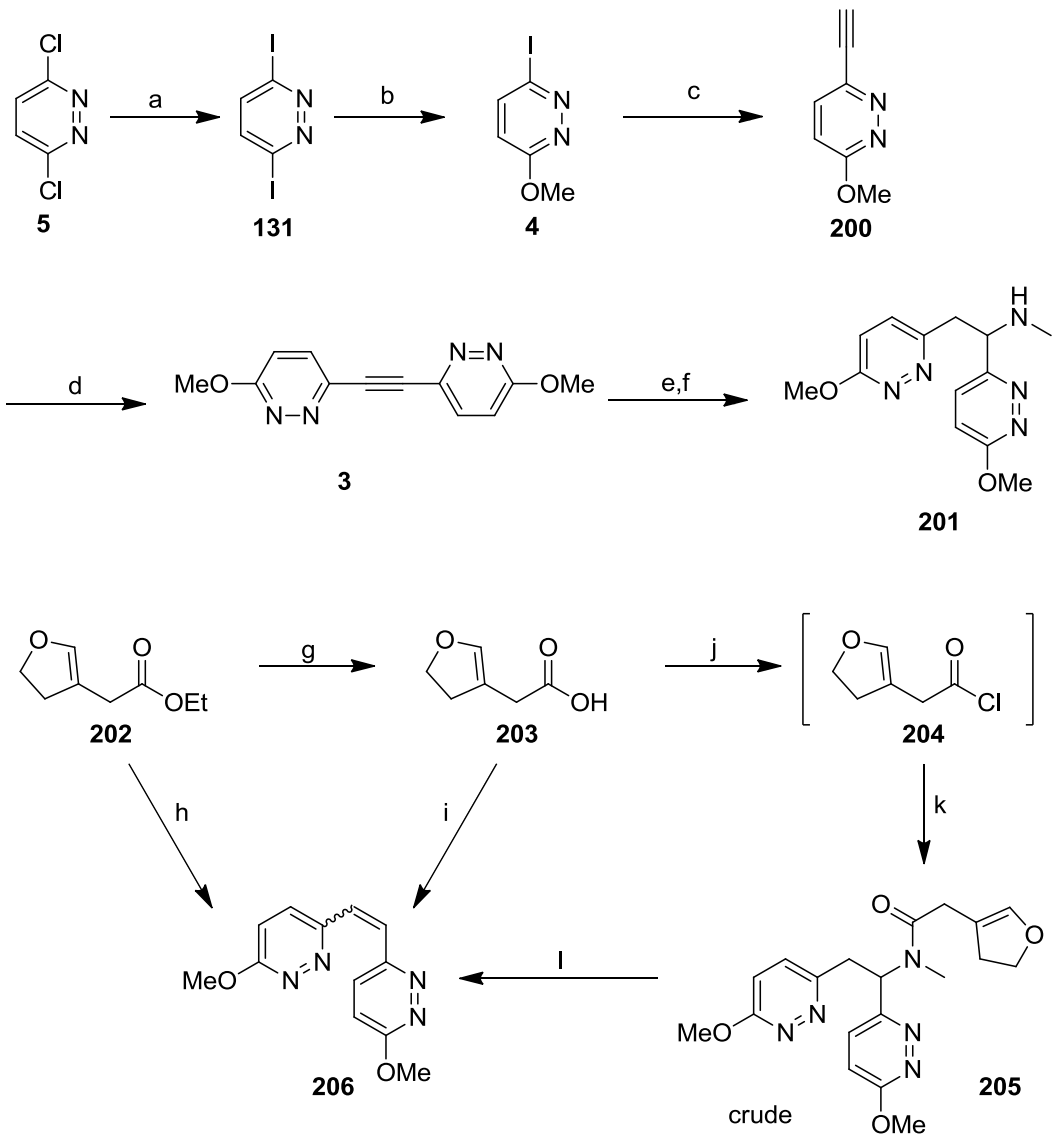


Figure 18. Diels-Alder strategy for the synthesis of thebaine.

The key intermediate **205** was synthesised to validate the Diels-Alder reaction. Unfortunately, **205** underwent an unexpected Hoffman-type elimination to give **206**, as shown in Scheme 35.



Scheme 35. Diels-Alder reaction attempt using a bis-pyridazine strategy.

Reaction conditions: a) HI, ICl (76%); b) MeOH, K_2CO_3 (72%); c) TMS acetylene, CuI, $PdCl_2(Ph_3)_2$, Et_3N, THF, then TBAF, THF, rt (69%); d) **4**, CuI, $PdCl_2(Ph_3)_2$, Et_3N, rt (71%); e) $MeNH_2$, Ind_2TiMe_2, toluene, 110 °C; (f) $NaBH_3CN$, MeOH, $ZnCl_2$ (68%, 2 steps); g) LiOH, MeOH, 50 °C; h) **201**, toluene, 150 °C; i) DMAP, Et_3N, **201**; j) oxalyl chloride, DMF; k) CDI, **201**, CH_2Cl_2, relux; l) toluene, reflux.

III. Discussion

III-1 Introduction

Based on the historical precedents reviewed in the previous chapter, it is decided to pursue several model studies towards the total synthesis of thebaine. As previously summarized one of the problems encountered in the past was the elimination of the methoxy pyridazine derivatives. Therefore it is decided to focus on simple model studies, which would allow to quickly assessing the feasibility of the intramolecular Diels-Alder strategy. The pyridazine will serve as diene, as shown in figure 19.

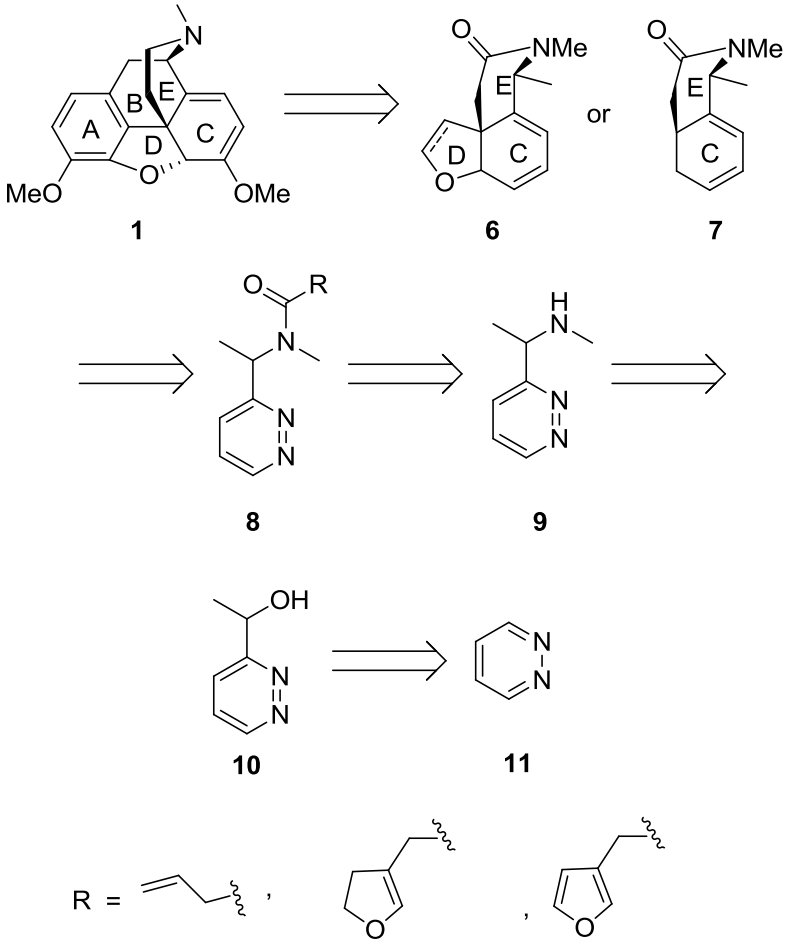


Figure 19. Retro analysis for simple model studies of thebaine.

The results of these studies are discussed in detail in the following section.

III-2 Model study to construct C and E ring of thebaine

In order to determine the viability of intramolecular Diels-Alder reaction to construct the C and E ring of thebaine, compound **207** was envisioned to undergo a Diels-Alder reaction to produce compound **7**, as shown in figure 20.

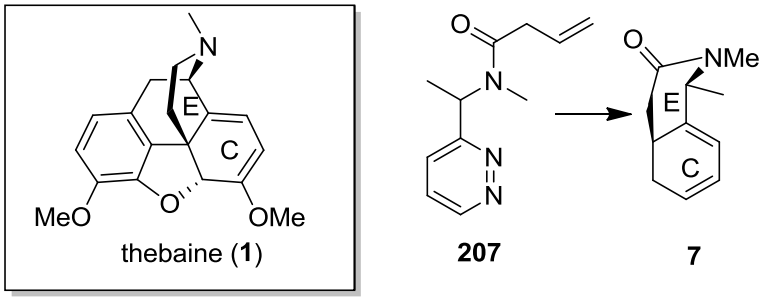
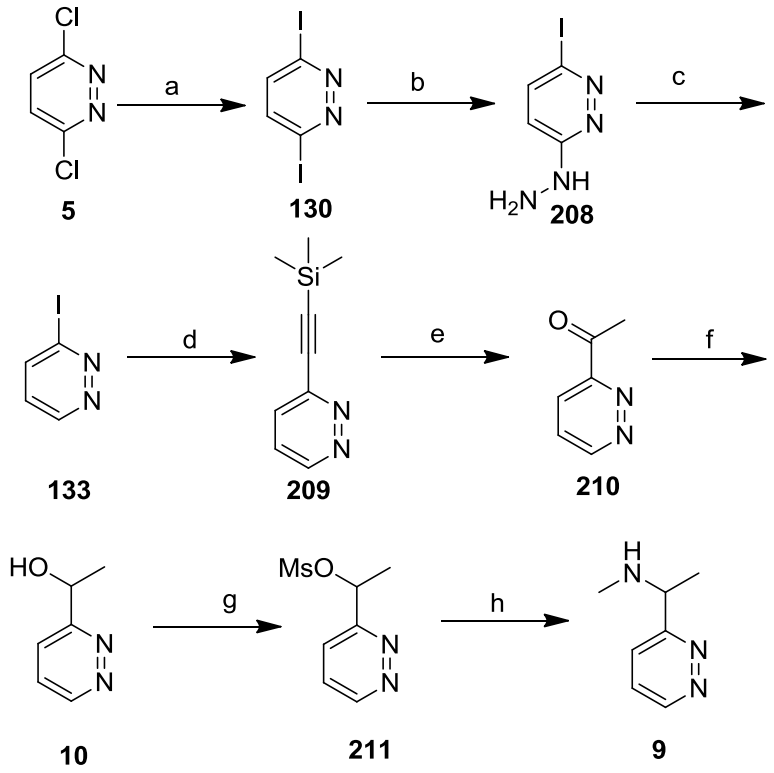


Figure 20. Model study to construct the C and E rings of thebaine**.**

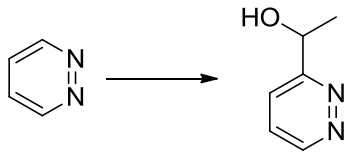
Compound **207** was prepared from compound **9** and **213**. Key intermediate **9** was synthesized by two routes. One route was found to be tedious and a low yielding process in which **9** was synthesised in 8 steps with an overall yield of 11%. Its synthesis started with a commercially available compound **5** and 3-iodopyridazine prepared according to literature procedures[38,39]. Compound **209** was synthesized through a general Sonogashira reaction and then subjected to an oxymercuration-demercuration reaction to get compound **210**. This keto derivative was reduced to **10** through a borohydride reduction. Then it was converted into key compound **9** in another 2 steps, as shown in Scheme **36**.



Scheme 36. Synthesis of pyridazine amine **9** from pyridazine **5**

Reaction conditions: a) KI, ICl, (72%); b) EtOH, reflux, $N_2H_4.H_2O$ (90%) c) HgO(yellow), H_2O, rt (75%); d) TMS acetylene, $PdCl_2(PPh_3)_2$, CuI, NEt_3, THF, rt (85%); e) $HgSO_4$, H_2SO_4, THF, H_2O, reflux (49%); f) $NaBH_4$, MeOH, rt (83%); g) MsCl, NEt_3, DCM; h) $MeNH_2$, DCM, THF (66%).

In another route, key compound **9** was prepared in three steps with an overall yield of 38% and this route was found to be reliable in order to carry forward the model studies. The key step in this route was the selective ortholithiation of pyridazine **11**. Literature procedure was a low yielding reaction of this step (26%).[25] Slight modification gave an improved yield of compound **10,** as shown in Table 1.



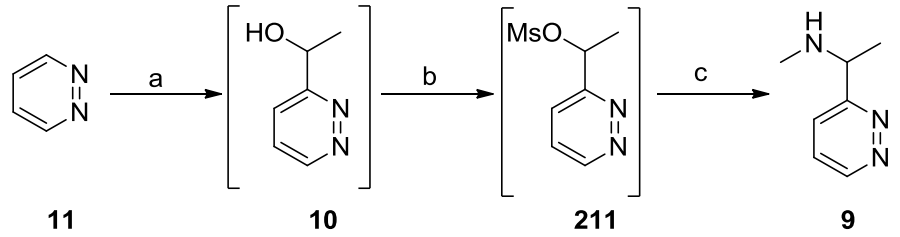
11 **10**

Figure 21. Ortholithiation of pyridazine.

Table 1. Different conditions for improving the yield of compound **10**.

Conditions	**Result**
TMEADA, *n*BuLi, THF, -78 °C, 1hr	Decomposition of starting material
TMEADA, *n*BuLi, THF, -78 °C to 0 °C , 1hr	Decomposition of starting material
TMEADA, *n*BuLi, THF, 0 °C to rt, 1hr	Decomposition of starting material
LiTMP, THF, -78 °C to 0 °C, 2 hr	Decomposition of starting material
*n*BuLi, THF, DMAE, -78 °C, 1 hr	Decomposition of starting material
LiTMP, THF, -85 °C, 1hr	39%

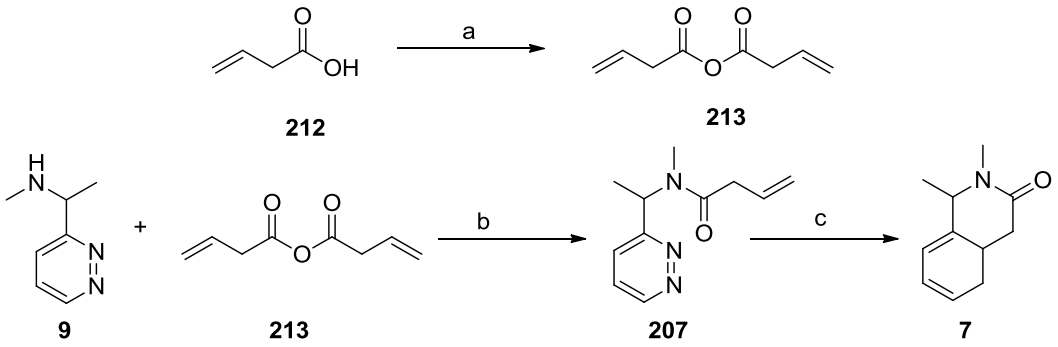
Furthermore, it was found that without isolating compounds **10** and **211**, isolated yield of pyridazine amine derivative **9** was improved with an overall yield of 38%, as shown in Scheme 37.



Scheme 37. Synthesis of pyridazine amine **9** from pyridazine **11**.

Reaction conditions: a) LTMP, THF, CH_3CHO, -85 ^oC; b) MsCl, Et_3N, CH_2Cl_2, 0 ^oC to RT; c) $MeNH_2$, CH_2Cl_2, THF, -75 ^oC to rt.

Vinyl acetic acid anhydride **213** was prepared according to a literature procedure[40] and coupled with pyridazine amine **9** in the presence of DMAP to get the Diels-Alder precursor. The Diels-Alder reaction occurred smoothly at reflux in *o*-xylene, as shown in scheme 38.



Scheme38. Diels-Alder successful attempt.

Reaction conditions: a) CH_2Cl_2, DCC, rt (69%); b) DMAP, Et_3N, CH_2Cl_2, rt (71 %); c) *o*-xylene, reflux (50%).

After validating the Diels-Alder reaction, a more complicated model study was designed, which is discussed in next section.

III-3 Model study to construct D, C and E ring of thebaine

The furanyl ester derivative **202** was chosen for further model studies as a dienophle to construct the C, D and E ring of thebaine with pyridazine amine **9**.

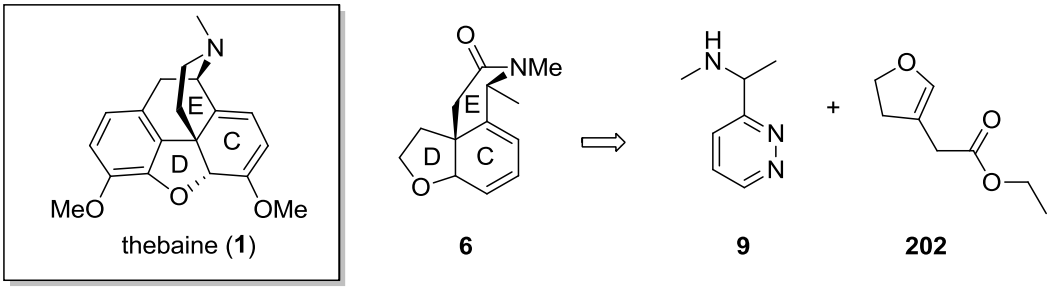
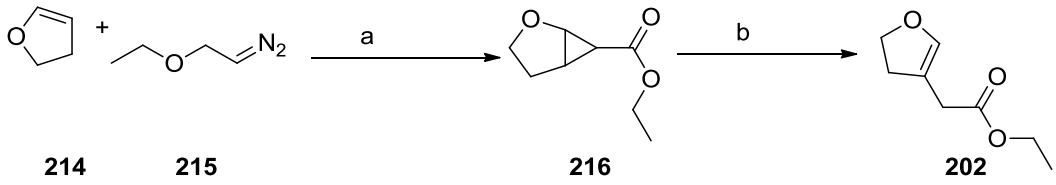


Figure 22. Model study with dihydrofuran ester.

202 was prepared according to a procedure already established in the group, starting from 2,3-dihydrofuran. The furan **214** was reacted with ethyldiazoacetate **215**, which was added drop wise over a 24 h span, to get cyclopropane intermediate **216**. Treatment with copper bronze afforded the ring opened ester **202** in a 53% overall yield, as shown in Scheme 39.



Scheme 39. Dihydrofuran ester synthesis.

Reaction conditions: a) Cu (Bronze), 65 ^{o}C, 24 hr (68%); b) Cu (Bronze), 150 ^{o}C, 16 hr, (63%).

Once ester **202** was obtained, several attempts were made to achieve amide coupling with *N*-methyl-1-(pyridazin-3-yl)ethanamine **9** but all attempts failed, as shown in Table 2.

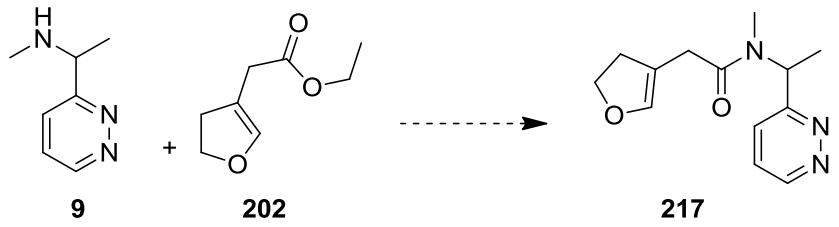
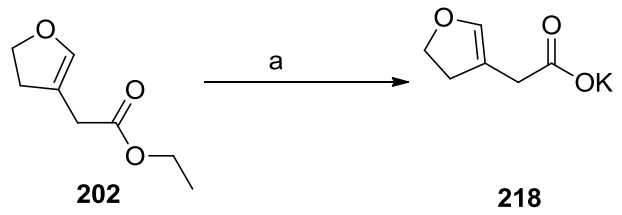


Figure 23. Attempted condition to make compound **217.**

Table 2. Attempted conditions to make compound **217**.

Condition	**Results**
Neat, 100 to 200 ^{o}C	Decomposition of starting material
DBU, triazole, neat, RT to 160 ^{o}C	Ester was consumed, **9** (35%) was recovered
DBU, triazole, trichlorobenzene, RT to 170 ^{o}C	Ester was consumed, **9** (26%) was recovered
DBU, triazole, DMF, RT to 160 ^{o}C	**9** (58%) was recovered
n-BuLi, THF used to make anion of amine, then ester was added to amine reaction mixture at -78 ^{o}C, temperature raised to till reflux with TLC monitoring.	No reaction

At this point compound **202** was converted into the corresponding acid salt **218**, as shown in Scheme 40.



Scheme 40. Synthesis of a potassium salt of dihydrofuranester.

Reaction conditions: a) KOH, EtOH, 50 ^{o}C, 16 hr (quantitative).

A mixed anhydride strategy was envisioned and pyridazine amine was attempted to achieve amide coupling with ester **202,** but an undesired product lactone **221** was formed, as shown in Figure 24 and Table 3.

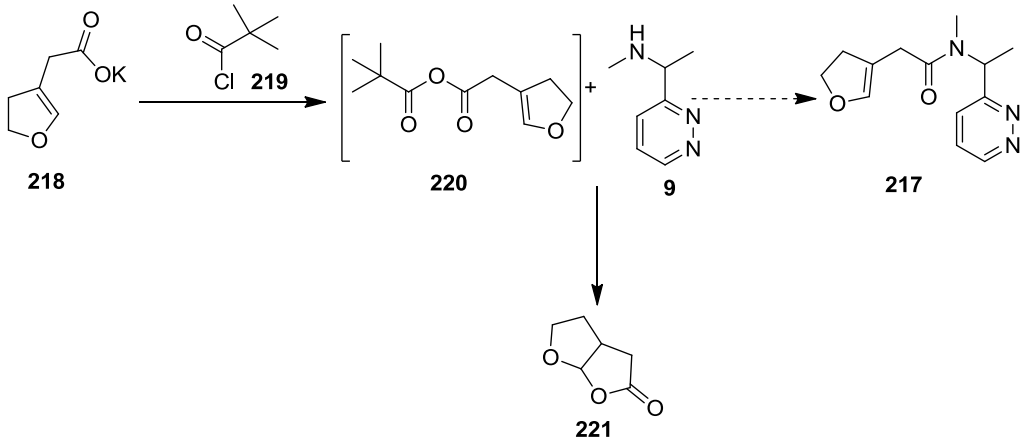
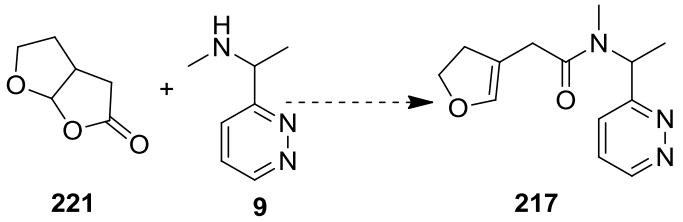


Figure 24. Mixed anhydride strategy to get an amide.

Table 3. Conditioned to synthesise the **217** with a mixed anhydride strategy.

Condition	**Result**
Pyridine, DCM, 0 ^{o}C to rt, 24 h, filetered through Celite, then DMAP, Et_3N and **9** were added	**220** was isolated
Pyridine, DCM, 0 ^{o}C to rt, 24 h then **9** was added	**220** was isolated

As none of the reactions gave the desired Diels-Alder precursor **217**, a lactone was chosen as a coupling partner with pyridazine amine **9,** but all attempts failed to synthesize the desire compound **217,** as shown in Table 4.

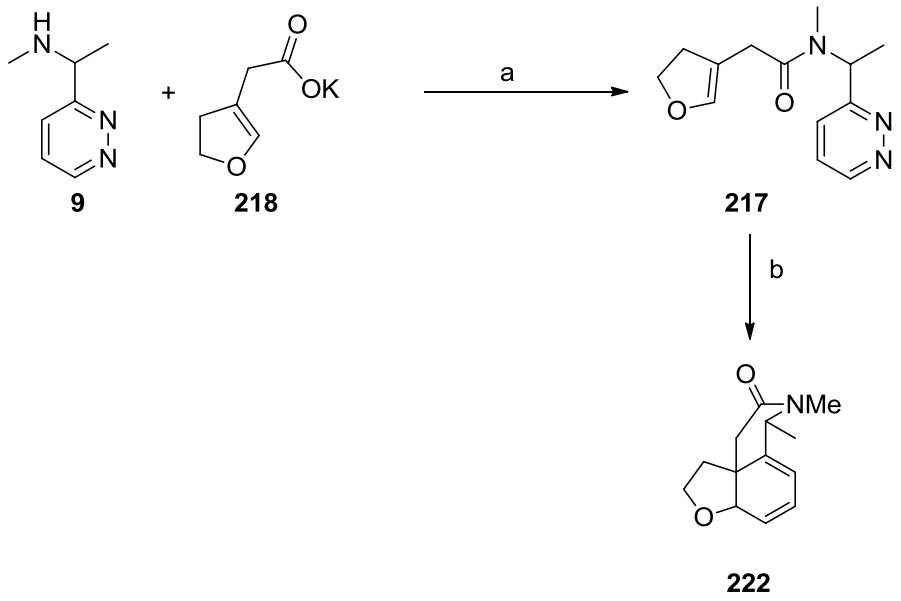


221 **9** **217**

Table 4. Conditioned to synthesise the **217** with lactone.

Condition	**Result**
DBU, Triazole, $CDCl_3$, reflux	**9** was recovered
Toluene, DMAP, reflux	**9** was recovered
DMF, DMAP, reflux	**9** was recovered

Finally, potassium salt **218** coupled with pyridazine **9** in the presence of HBTU gave the desired Diels-Alder reaction precursor **217** which underwent a Diels-Alder reaction at 200 ^{o}C, as shown in Scheme 41.



Scheme 41. Diels-Alder reaction precursor **217** which underwent an intramolecular Diels-Alder reaction to yield **222**.

Reaction conditions: a) HBTU, DIPEA, DMF, RT, 48 hr (69%); b) 1,2,4 trichlorobenzene, 200 °C, 14 hr (58%).

After this model study, furan acetic acid was chosen as a dienophile for the Diels-Alder reaction. A few examples that are present in literature prove that furan can act as a dienophile.[41,42] With this fact, another model study is envisioned, as shown in Figure 25.

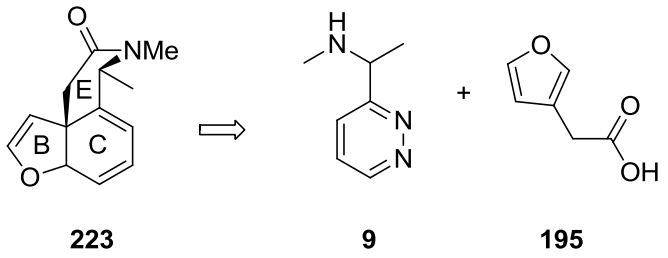


Figure 25. Model study with **9** and **195**.

If compound **223** was formed, then another double bond of **195** could be used for a second Diels-Alder reaction with **201** in the synthesis of thebaine as shown in Figure 26.

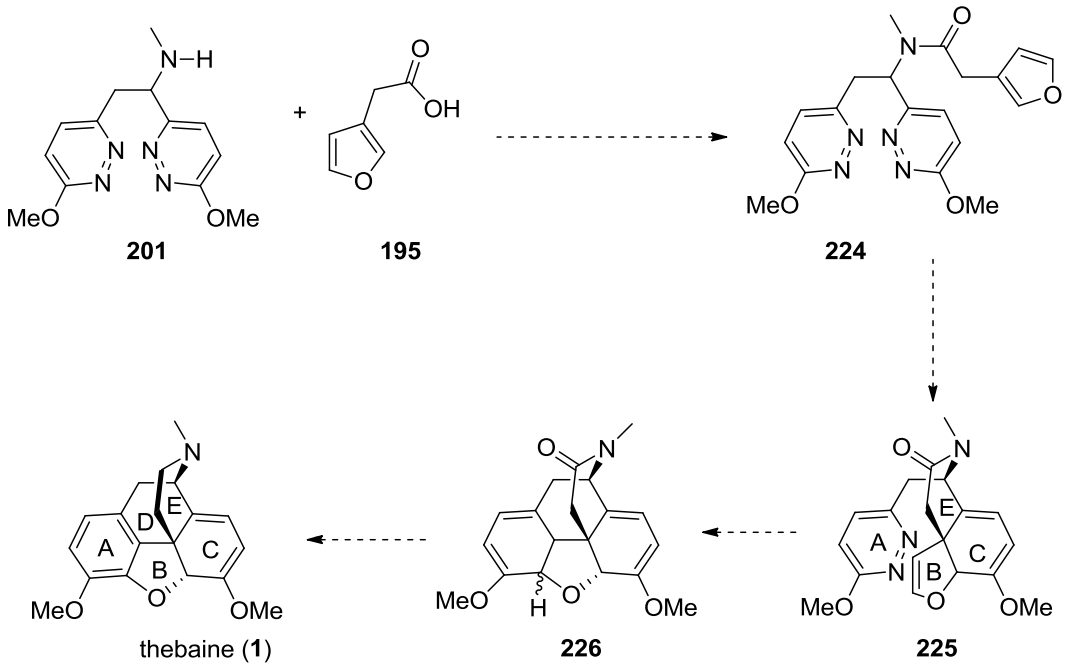
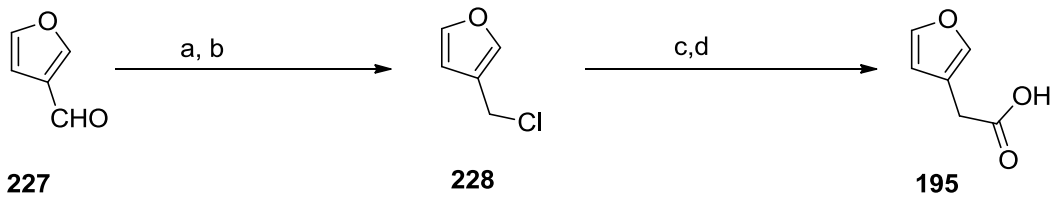


Figure 26. Furan strategy towards the synthesis of thebaine

Recently, it was proven that furan can act as dienophile and can undergo Diels-Alder reactions with 1,2-diazine derivatives in the presence of bidentate borane Lewis acids.[43]

With this vision, 2-furanyl acetic acid **195** was prepared in four steps from furan-3-carboxaldehyde according to a published procedure, as shown in Scheme 42.[44]

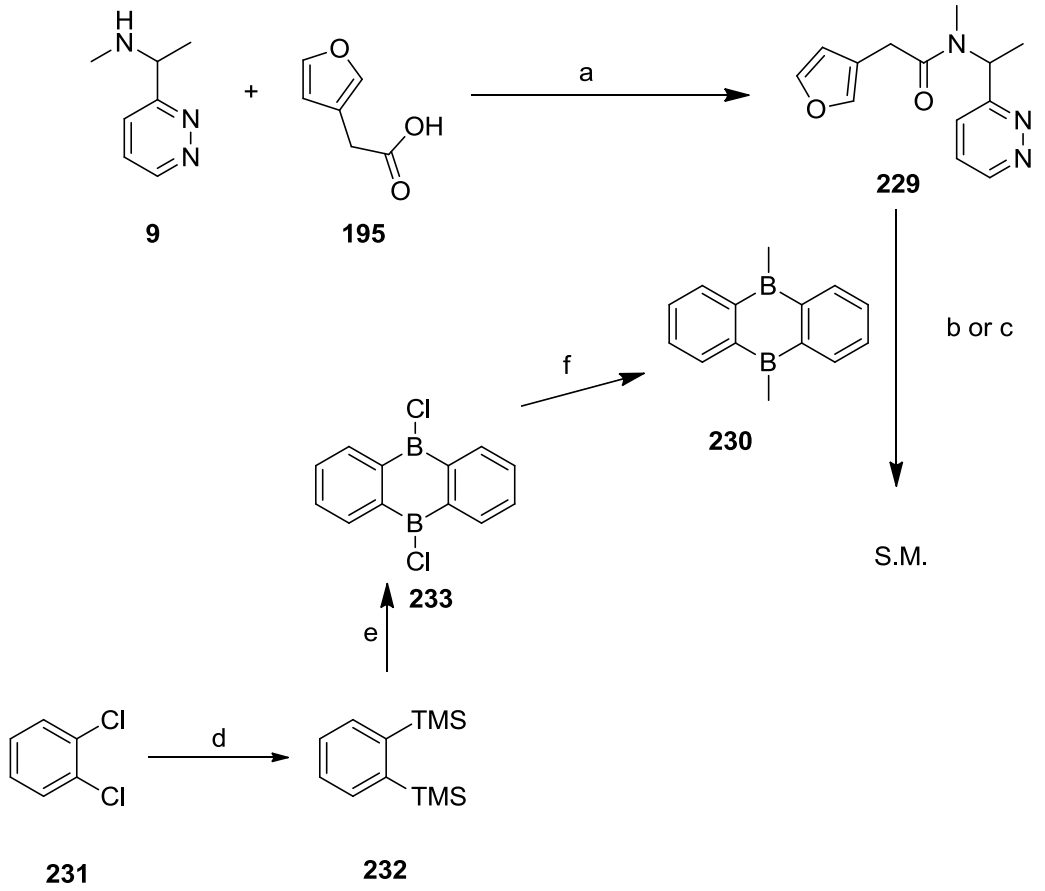


227 **228** **195**

Scheme 42. Synthesis of furan acetic acid.

Reaction conditions: a) $NaBH_4$, *i*PrOH; b) $SOCl_2$, Pyr; c) NaCN, H_2O, DMSO; d) aq. KOH (6.2% in 4 steps).

Compound **195** was then coupled with pyridazine **9** to get compound **229**. Compound **229** was subjected to a Diels-Alder reaction in the presence of diboran catalyst **230** which was prepared according to the literature procedure.[45,46] Unfortunately, cyclization failed to occur even at a high temperature, as shown in Scheme 43.

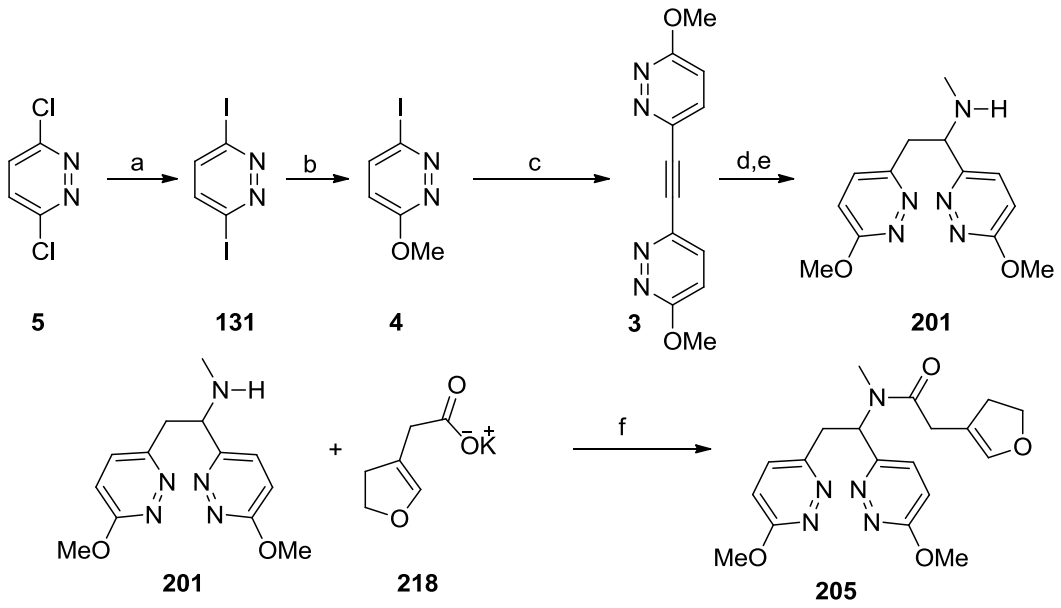


Scheme 43. Attempted Diels-Alder reaction with **229**.

Reaction conditions: a) HBTU, DIPEA, DMF, RT, 48 hr, 63%; b) Diglyme, DIPEA, 150-280 °C; c) 1,2,4 trichlorobenzene DIPEA, 150-300 °C ; d) TMSCl, Mg, HMPA, 100 °C (74%); e) BCl_3, 1,2-DCE, 140 °C (61%); f) $AlMe_3$, Hexane, rt (21%).

III-4 Model studies using a bis-pyridazine derivative

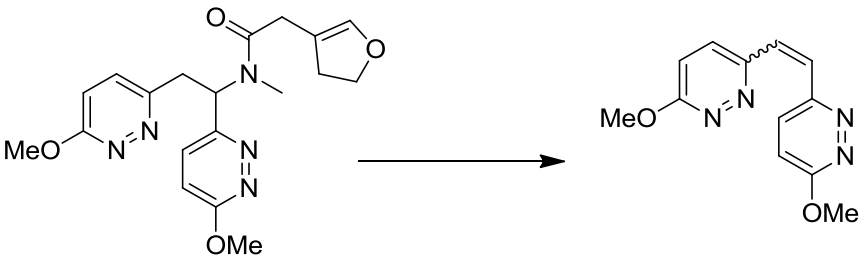
With the success of simple model studies, a previously stabilised route was followed to synthesise bis-pyridazine derivative **201**. **201** was coupled with compound **218** in presence of HBTU as shown in scheme 44.



Scheme 44. Synthesis of Bis-pyridazine derivative.

Reaction conditions: a) HI, ICl (81%); b) MeOH, reflux (52%); c) acetylene, $Pd(OAc)_2$, CuI, Et_3N (68%); d) $MeNH_2$, $TICl_4$, $^tBuNH_2$, toluene, 80 °C; e) $NaBH_3CN$, $ZnBr_2$, THF, rt (63% in two steps); f) HBTU, DIPEA, DMF, rt, 48 h (89%).

This Diels-Alder precursor (**205**) was reinvestigated for 4+2 cycloaddition. Unfortunately, the thermal Diels-Alder reaction in a different condition, microwave reaction and Lewis acid catalysed Diels-Alder reaction failed to give the desired cycloadduct product, as shown in Scheme 45.



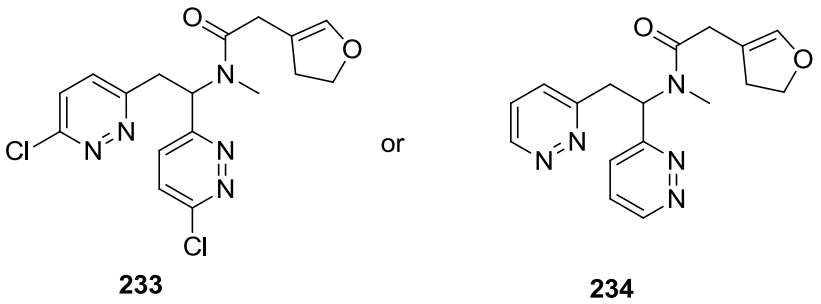
205 **206**

Condition
1,2,4-trichlorobenzene, 100 ºC
Benzene, 160 ºC
Me_2AlCl, Benzene, 135 ºC
$BF_3{\cdot}OEt_2$, Benzene, 160-170 ºC
Microwave irradiation (Benzene), 150 ºC

Scheme 45. Diels-Alder reaction attempt of **205** in different condition.

Probably the methoxy group was donating the electrons to the ring of **205** and accelerating the elimination reaction to get a more stable pyridazine alkene **206**.

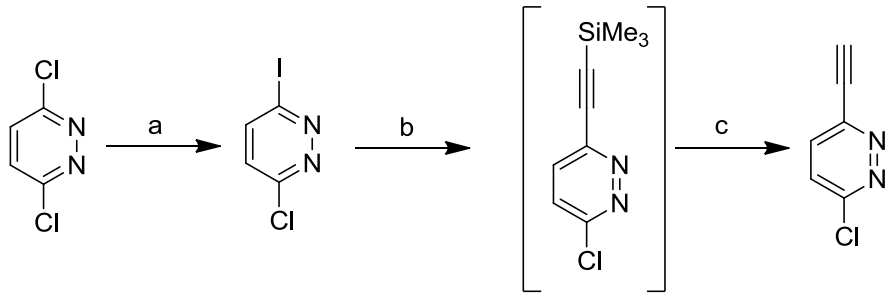
To prevent the elimination problem, two model compounds **233** and **234** were envisioned in which the methoxy group could be replaced by H or Cl groups, as shown in Figure 27.



233 **234**

Figure 27. Bis-pyridazine-based model compounds.

Pyridazine **235** was prepared according to the literature procedure.[47] **235** was subjected to a standard Pd-catalyzed Sonogashira reaction and the removal of the silyl protecting group gave the compound **237,** as shown in Scheme 46.

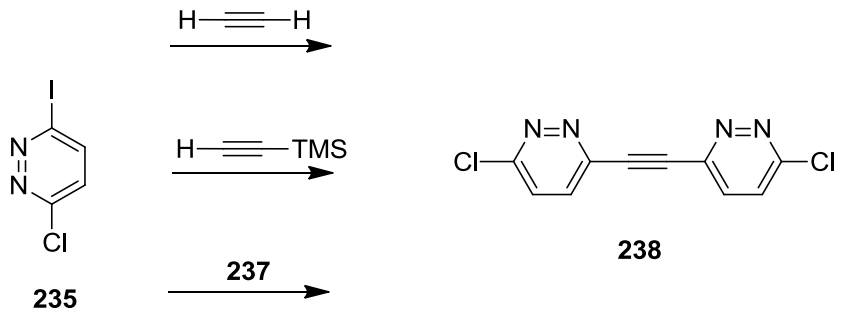


5 **235** **236** **237**

Scheme 46. Synthesis of compound **237**.

Reaction conditions: a) NaI, HI (71%); b) $PdCl_2(PPh_3)_2$, Et_3N, CuI, THF; c) TBAF, THF (71% in 2 steps).

The pyridazine **235** was subjected to a variety of cross coupling reactions with acetylene, TMS-acetylene and **237**, but none of them gave the desired compound **238** in a reasonable yield and **238** was found to be really unstable, as shown in Scheme 47.

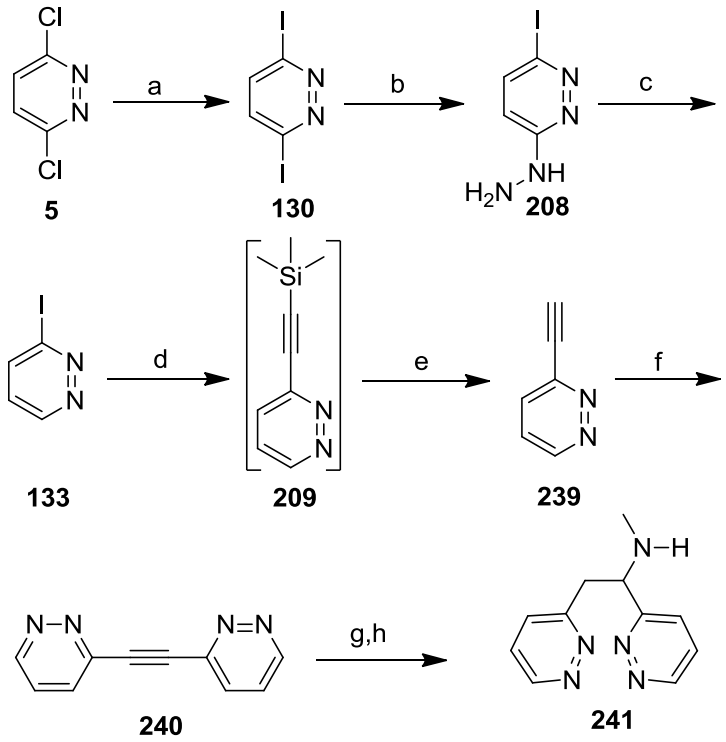


Scheme 47. Attempted Cross-coupling reactions.

Conditions
$PdCl_2(PPh_3)_2$, Et_3N, CuI, THF, **237**
$Pd(dba)_2$, Bu_4NOAc, DMF, **237**
$Pd(OAc)_2$, Bu_4NOAc, DMF, **237**
NaH, THF, **237**
TMS-acetylene, $PdCl_2(PPh_3)_2$, DBU, CuI, Benzene, Water
TMS-acetylene, $PdCl_2(PPh_3)_2$, DBU, CuI, Benzene
Acetylene, $PdCl_2(PPh_3)_2$, Et_3N, CuI, THF
Acetylene, $Pd(PPh_3)_4$, Bu_4NOAc, CuI, THF
Acetylene, $Pd(PPh_3)_4$, Bu_4NOAc, CuI, Dioxane
Acetylene, $Pd(OAc)_2$, PPh_3, Bu_4NOAc, CuI, Dioxane
Acetylene, $Pd(OAc)_2$, PPh_3, Et_3N, CuI, MeCN:H_2O (3:1)
Acetylene, $PdCl_2(PPh_3)_2$, PPh_3, Et_3N, CuI, MeCN:H_2O (3:1)

The structure of **238** was confirmed only by ^1H NMR and mass spectroscopy. In parallel, 3-iodo pyridazine **133** was prepared according to the literature procedure in 3 steps.[37,38] Dipyridazine alkyne **240** as prepared in another

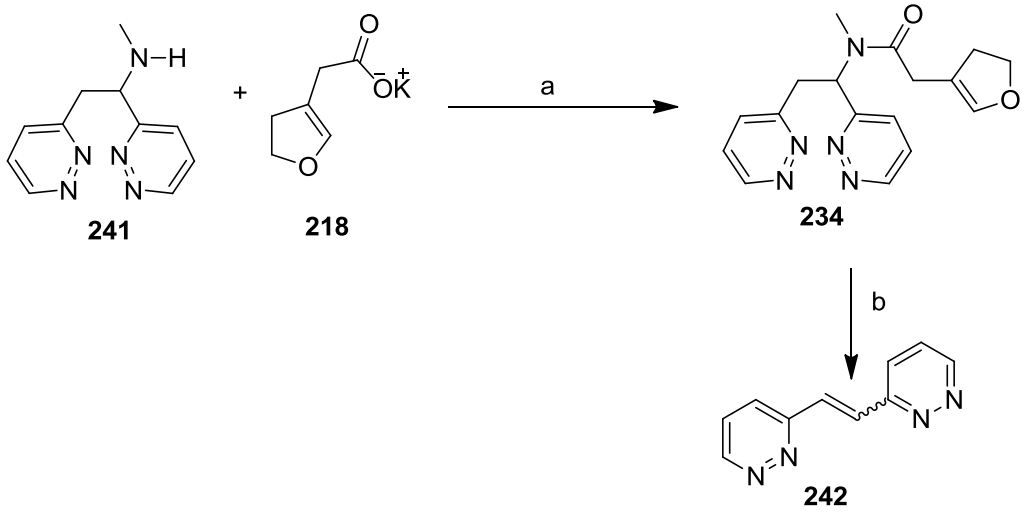
3 steps and it was carried forward for the model studies. Initially, the hydroamination of **240** with different catalyst like $TICl_4$ with $^tBuNH_2$, AgOTf and $AgNTf_2$ did not give the desired product **241**. However, the hydroamination with $Ti(NMe_2)_4$ gave the desired product, as shown in Scheme 48.



Scheme 48. Bis pyridazine amine synthesis.

Reaction conditions: a) KI, ICl (73%); b) EtOH, reflux, $N_2H_4.H_2O$; c) HgO(yellow), H_2O, rt (61% in 2 steps); d) TMS acetylene, $PdCl_2(PPh_3)_2$, CuI, NEt_3, THF, rt; e) TBAF, THF (74% in 2 steps); f) $PdCl_2(PPh_3)_2$, Et_3N, CuI, THF, **139** (51%); g) $Ti(NMe_2)_4$, toluene, $MeNH_2$; h) $NaBH_3CN$, $ZnCl_2$, MeOH (41% in two steps).

Bis-pyridazine amine was coupled with **218** and then **234** subjected to a Diels-Alder reaction in a sealed tube in toluene at 150 °C and provided only the elimination product **243**, as shown in Scheme 49.



Scheme 49. Unexpected elimination reaction of **234**.

Reaction conditions: a) COMU, DIPEA, DMF, rt, 22 h (73%); b) 1,2,4-trichlorobenzene, 150 °C (71%).

IV. Conclusions and Future Work

The establishment of intra-molecular Diels-Alder cycloaddition reactions involving pyridazine and a suitable dienophile through model studies showed promise as a potential route towards the synthesis of thebaine. However, investigations towards the synthesis of thebaine using a bis(pyridazine) framework have proven unsuccessful, as an unexpected Hofmann-type elimination occurred.

Recently, radical cation [4+2] cycloaddtion reactions have been done of thermally unactive cycloaddtion reactions.[48] It might overcome the problem of

Hoffman type elimination of compound **234**. Future work needs a radical cation Diels-Alder strategy or a more refined route to overcome the Hofmann-type elimination.

For a new route, instead of using a bis(pyridazine) for an intra-molecular Diels-Alder cyc1oaddition reaction, a single pyridazine moiety can be used for the first Diels-Alder reaction and another pyridazine ring can be attached later for another Diels-Alder reaction, as shown in Figure 28.

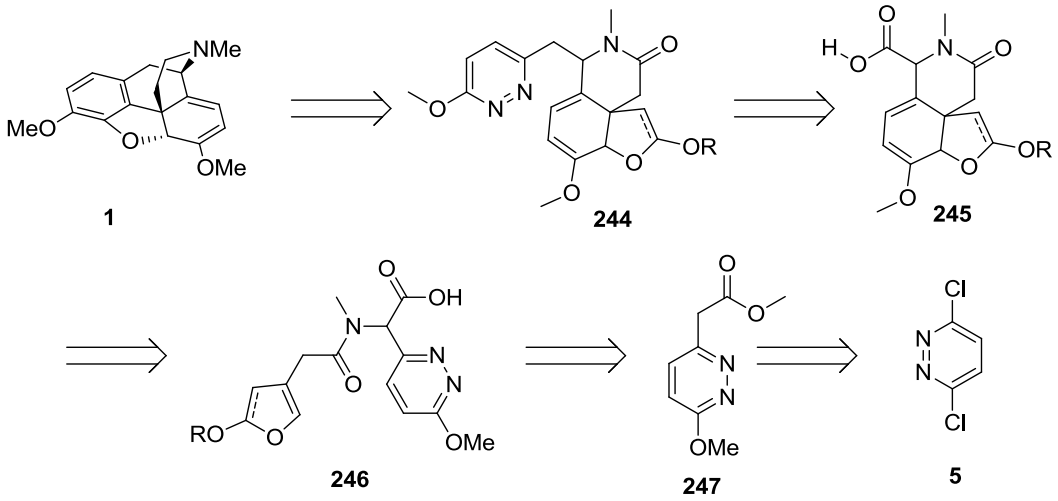
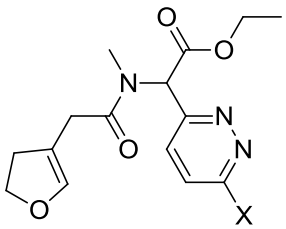


Figure 28. Retro synthetic analysis based on the first Diels-Alder reaction.

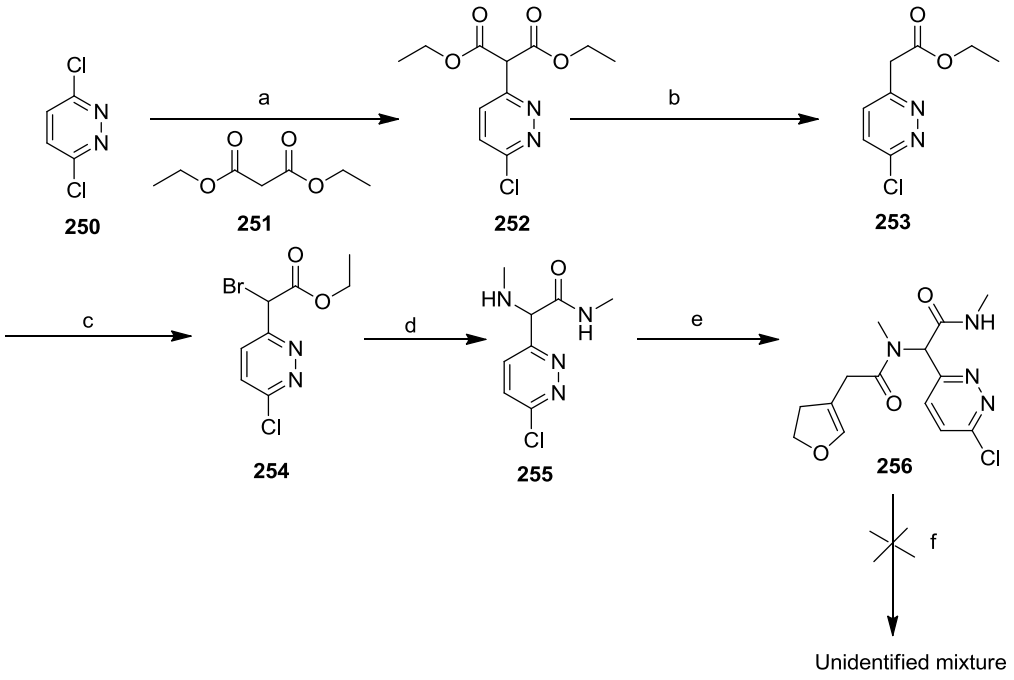
As the synthesis relied on the first intramolecular Diels-Alder reaction, simple model compounds were envisioned which could allow quickly assess the feasibility of the Diels-Alder reaction, as shown in Figure 29.



X = OMe (**248**)
= H (**249**)
= Cl (**250**)

Figure 29. Envisioned Diels-Alder precursor compounds.

With this vision, the Diels-Alder precursor **250** was chosen, which become available in a short number of steps from commercially available dichloropyridazine **5**. Compound **5** was converted into pyridazine ethyl ester derivative **252** in two steps. At this point, **252** was brominated at the benzylic position and then treated with methylamine. Unfortunately, the methylamine displaced both the bromine and ester which resulted in compound **254.** Compound **254** was subjected to a Diels-Alder reaction without any success, as shown in Scheme 50.



Scheme 50. Diels-Alder attempt with compound **256**.

Reaction conditions: a) Cs_2CO_3, DMSO, 110 °C; b) DMSO, NaCl, H_2O, 140 °C (43% in two steps); c) $NaBrO_3$, $NaHSO_3$, EtOAc, H_2O, rt; d) $MeNH_2$, THF, -78

°C to rt (65% in 2 steps); e) HBTU, DIPEA, DMF, rt, 22 h (58%); f) 180-220 °C, 1,2,4-trichlorobenzene.

Currently, we are focussing on synthesizing the Diels-Alder precursor **249**, as shown in figure 30.

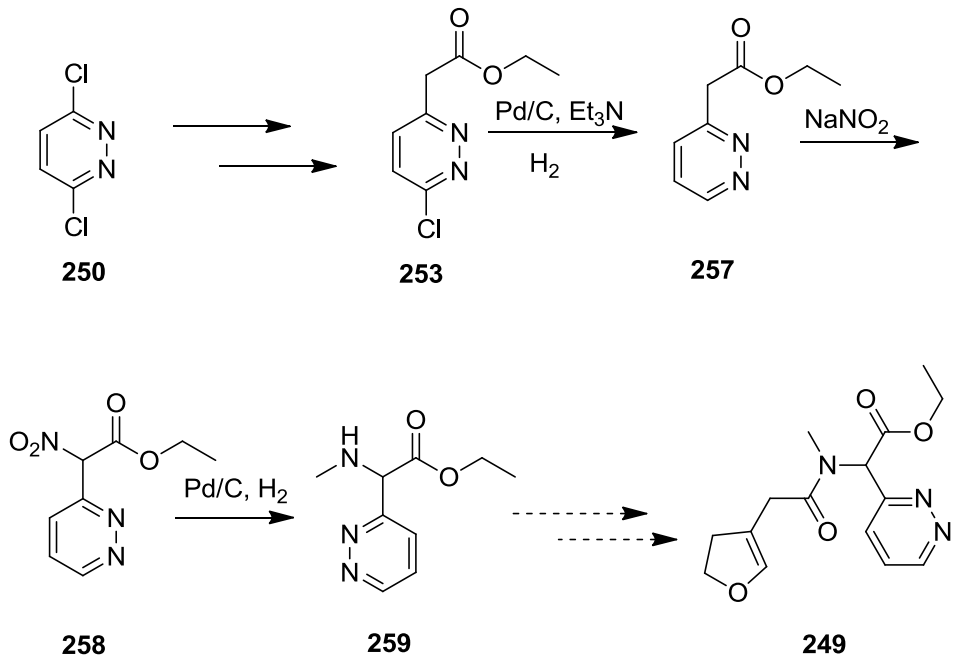


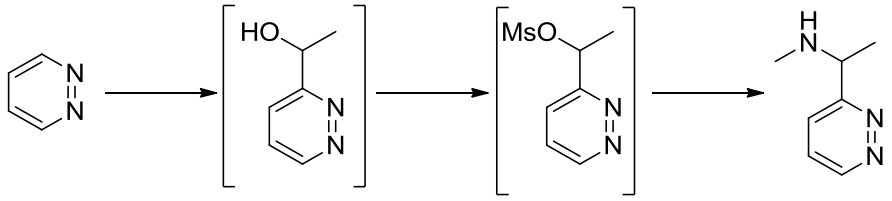
Figure 30. Future Diels-Alder precursor compounds.

V. Experimental Section

V-1 General Experimental Details

All non-hydrolytic reactions were carried out under an argon atmosphere. Glassware used for moisture-sensitive reactions was flame-dried under vacuum and subsequently purged with argon. THF was distilled from potassium/benzophenone. Methylene chloride and acetonitrile were distilled from calcium hydride. FlashColumn Chromatography was performed using Kieselgel 60 (230-400) mesh. Melting points were measured on a Thomas-Hoover melting point apparatus and are reported uncorrected. IR spectra were obtained on a Perkin-Elmer FT-IR 1600 Series Spectrum One instrument and were recorded as neat samples. ^{1}H and ^{13}C NMR spectra were obtained on either a 300-MHz Bruker or a 600 MHz Varian instrument. Combustion analyses were performed by Atlantic Microlabs, Norcross, Georgia, USA.

V-2 Detailed Experimental Details



Synthesis of *N*-methyl-1-(pyridazine-3-*yl*) ethanamine (9):

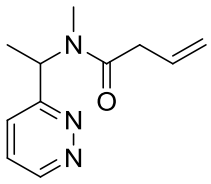
In a flame-dried round bottom flask, under argon atmosphere, tetramethylpiperidene (2.07 mL, 10.0 mmol) was added in THF (74 mL). *n*-BuLi (2.26 M in Hexanes, 10.0 mmol) was added at -30 °C then slowly allowed to warm untill 0 °C and left for 0.5 h at 0 °C. Pyridazine (1.05 g, 10.0 mmol) was added at -85 °C dropwise followed by adding acetaldehyde (2.69 mL, 50.0 mmol) at -85 °C. Reaction was quenched with 3.6 mL of a HCl/ THF/ EtOH (1:1:1) mixture after 1.5 h under inert atmosphere. The reaction mixture was left to warm to room temperature then a saturated solution of sodium bicarbonate was added to make the reaction mixture slightly basic (pH = 8). Concentrated under vacuum and extracted with CH_2Cl_2 (2 × 60 mL) then with $CHCl_3$:EtOH (4:1, 3 × 30 mL). The organic layer was washed with brine and dried with $MgSO_4$, filtrated, and concentrated under vacuum. Crude product **10** was isolated as a mixture and the structure was determined by ^{1}H NMR. Flash column chromatography: column ran with EtOAc/MeOH (5 to 8%) to afford 2.12 g of yellow oil. R_f = 0.43 in EtOAc/MeOH (90:10); ^{1}H NMR ($CDC1_3$, 300 MHz) δ: 9.00 (dd, J_1 = 5.0, J_2 = 10.1, 1H), 7.30-7.83 (m, 2H), 5.10 (q, J = 6.6 Hz, lH), 1.58 (d, J = 6.6 Hz, 3H).

Crude product **10** (2.12 g) was placed in a flame-dried round bottom flask, containing CH_2Cl_2 (50 mL), under inert atmosphere. At 0 $^{\circ}$C, triethylamine (4.71 mL, 3.40 mmol) was added followed by the addition of mesyl chloride (2 mL, 2.50 mmol). After 1.5 h, cold H_2O (5 mL) was added and the reaction mixture was transferred into a separatory funnel, and a 15 mL of cold saturated solution of sodium bicarbonate was added. The organic layer was separated and the aqueous layer was washed with CH_2Cl_2 (5 × 50 mL) followed washing with brine, then dried over $MgSO_4$, filtered and concentrated under vacuum. Crude product **211** was isolated as a mixture by flash column chromatography: silica-gel was neutralized with a mixture of EtOAc/Hexane/TEA (9:1:0.5) and column ran with an EtOAc/Hexane/TEA (9:1:0.05) eluent to afford 1.80 g of a crude product **211** as a yellow liquid. R_f = 0.32 in EtOAc/Hexane (9:1); ^{1}H NMR ($CDC1_3$, 300 MHz) δ: 9.14 (dd, J_1 = 5.0, J_2 = 10.1, 1H), 7.26-7.69 (m, 2H), 6.01 (q, J = 6.6 Hz, lH), 3.02 (s, 3H), 1.81 (d, J=6.6 Hz, 3H).

Crude product **211** (1.80 g) was dissolved in 8 mL of CH_2Cl_2 and placed in a flame-dried, sealed tube. THF (10ml) was added and the temperature was decreased to - 75 $^{\circ}$C. Excess methylamine gas was bubble into the reaction mixture and left at rt for 48 h. Concentrated, diluted with 20 mL of EtOAc, made basic with sodium carbonate solution (5mL). The organic layer was separated and the aqueous layer was washed with ethyl acetate (3 × 30 mL) and then with $CHCl_3$/EtOH (4:1, 3 × 30 mL). The organic layer was washed with brine and dried with $MgSO_4$, filtered and concentrated under vacuum. Product **9** was isolated by flash column chromatography: the column was run with

CH_2Cl_2/MeOH/ NH_3 (95:5:1) as the eluent and then CH_2Cl_2/MeOH/$NH_{3(aq.)}$ (95:8:1) to afford 1.13 g (38 % overall yield) of compound **9** as a yellow oil which darkened when exposed to air.

Compound **9:** R_f = 0.1 in CH_2Cl_2/MeOH/$NH_{3(aq.)}$ (95:5:2); IR (film) ν = 3400, 3063, 2974, 2879, 1582, 1556, 1452, 1435, 823, 761 cm^{-1}; ^1H NMR ($CDC1_3$, 300 MHz) δ: 9.08 (dd, J_1 = 5.0, J_2 = 10.1, 1H), 7.28-7.57 (m, 2H), 4.02 (q, 1H), 2.33(s, 3H), 1.45 (d, J = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 22.4, 34.4, 59.8, 124.7, 126.9, 150.4, 166.2; HRMS-FAB calcd for $C_7H_{12}N_3^+$: 138.1015, found 138.1031. Anal. Calcd for dioxalate salt of **9,** $C_{16}H_{24}N_6O_4$.1/4CH_3OH: C, 52.74; H, 6.64; found C, 52.41; H, 6.77.

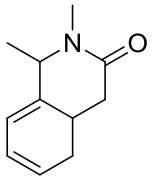


Synthesis of 1, 2-dimethyl-1, 2, 4a, 5-tetrahydroisoquinolin-3(4*H*)-one (207):

In a flame-dried round bottom flask, under inert atmosphere, pyridazine (0.05 g, 0.36 mmol) and DMAP (0.02 g, 0.14 mmol) were placed. Freshly distilled DCM (1.5 mL) was added, forming a pale-yellow solution, followed by the addition of triethylamine (0.15 mL, 1.09 mmol), and the stirred mixture was cooled down to 0 ºC. After 10 min vinyl acetic acid anhydride (0.69 mL, 0.73 mmol) was added in a drop-wise fashion. After 1 h in an ice-bath the reaction mixture was left to warm to room temperature and stirred for 20 h. After this time the reaction

mixture was concentrated to dryness and the crude mixture was re-dissolved in DCM, washed with a saturated solution of sodium bicarbonate and the organic layer was dried with MgSO4, filtered and concentrated under vacuum. The product was isolated by flash column chromatography: silica-gel was neutralized with a mixture of EtOAc/MeOH/TEA (94:1:5) and the column was run with an eluent of EtOAc/MeOH/TEA (99:1:0.5) to afford 0.06 g (87%) of compound **7** as a light yellow oil.

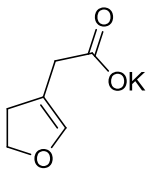
Compound **7**: R_f = 0.53 in EtOAc/MeOH (95:5); IR (film) ν = 3434, 2926, 1626, 1435, 1402, 1338, 1274, 1131, 1080, 997, 922 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ: 9.14-**minor rotamer** (d, J = 4.2 Hz, 1H), 9.09-**major rotamer** (dd, J_1 = 1.8, J_2 = 4.8 Hz, 1H), 7.49-7.39 (m, 2H), 6.12-6.02 (m, 1H), 5.99-5.89 (m, 1H), 5.18-5.08 (m, 2H,), 3.32-**minor rotamer** (dd, J_1 = 0.9 Hz, J_2 = 7.5 Hz, 2H), 3.16-**major rotamer** (dd, J_1 = 0.9 Hz, J_2 = 7.5 Hz ,2H), 2.89-**major rotamer** (s, 3H), 2.73-**minor rotamer** (s, 3H), 1.79-**minor rotamer** (d, J = 7.2 Hz, 3H), 1.67 -**major rotamer** (d, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 171.3, 161.7, 150.5, 131.0, 126.8, 126.6, 117.9, 51.8, 39.0, 30.1, 15.1; HRMS-EI calcd for $C_{11}H_{15}N_3O$: 205.1210, found 205.1215; Anal. Calcd for $C_{11}H_{15}N_3O$: C, 64.37; H, 7.37; found C, 64.12; H, 7.22.



Synthesis of 1, 2-dimethyl-1, 2, 4a, 5-tetrahydroisoquinolin-3(4*H*)-one (7):

In a flame-dried, Ar-flushed round bottom flask, pyridazine (35 mg, 0.17 mmol) was added. The reaction flask was evacuated and refilled with argon. This step was repeated a further two times then *o*-xylene (3mL, 0.06 M) was added under an argon atmosphere. The reaction mixture was left under reflux at 156° C for 26 hs. Then reaction mixture was cooled to rt and product **7** was isolated by flash column chromatography: first hexane (50 mL) was used as the eluent to remove *o*-xylene then 4:1 Hx/ EtOAc (100 mL) and 2:1 Hx/ EtOAc (100 mL) eluent mixtures were used to afford 14 mg (50%) of compound **7** as a light yellow oil.

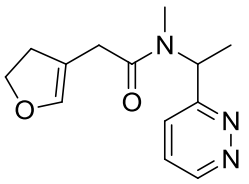
Compound **7:** R_f = 0.30 in EtOAc/MeOH (95:5); IR (film) ν = 2923, 2851, 1739, 1626, 1552, 1459, 754, 716 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ: 5.89-5.66 (m, 3H), 3.87-3.80(q, *J* = 6.6 Hz, 1H), 2.94 (s, 3H), 2.92-2.88(m, 1H), 2.85-2.04 (m, 4H), 1.36 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 169.8, 137.2, 124.3, 122.6, 117.8, 60.3, 38.9, 32.7, 29.1, 27.6, 20.1; HRMS-EI calcd for $C_{11}H_{15}NO$ (M^+): 177.1146, found 177.1153; Anal. Calcd for $C_{11}H_{15}NO$: C, 74.54; H, 8.53; found C, 74.27; H, 8.72.



Synthesis of potassium 2-(4, 5-dihydrofuran-3-yl) acetate (218):

In a flame-dried round bottom flask, under an argon atmosphere, the dihydrofuran ester (0.34 g, 2.18 mmol) was added in absolute EtOH (6 mL) followed by KOH (0.12 g, 2.18 mmol). Once the KOH dissolved in the EtOH, the temperature was raised to 54 ºC. After 16 h the reaction mixture was cooled to rt, concentrated and washed with pentane to afford 0.34 g of a light yellow solid compound **218** quantitatively.

Compound **218:** mp 195-197 ˚C (EtOH); IR (KBr) ν = 3411, 3122, 2969, 2898, 2852, 1563, 1388 cm^{-1}; ^{1}H NMR (D_2O, 300 MHz) δ: 6.13 (s, 1H), 4.25 (t, 2H, *J*= 9.3 Hz), 2.86 (d, 2H, *J*= 0.9 Hz), 2.49-2.59 (m, 2H); ^{13}C NMR (D_2O, 150 MHz) δ: 180.6, 140.2, 111.7, 70.1, 34.9, 31.6; HRMS-FAB calcd for $C_6H_7O_3K_2^+$: 204.9664, found 204.96582; Anal. Calcd for $C_6H_7O_3K \cdot 1/2\ H_2O$: C, 41.13; H, 4.55; found C, 41.20; H, 4.69.

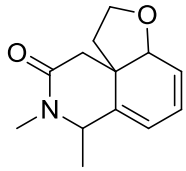


Synthesis of 2-(4,5-dihydrofuran-3-*yl*)-*N*-(1-pyridazin-3-ylethyl)acetamide (217):

In a flame-dried 25 mL round bottom flask, under an atmosphere of argon, activated molecular sieves (3 Å) were introduced followed by DMF (1 mL) and compound **218** (0.27 g, 1.64 mmol) at rt. Then diisopropylethylamine (0.47 mL, 2.73 mmol) and HBTU (0.50 g, 1.31 mmol) were successively added and stirred for 2.5 h. A solution of pyridazine **9** (0.15 g, 1.09 mmol) in DMF (2 mL) was added to the reaction mixture and the reaction was left overnight. Then reaction mixture was filtered through a celite plug which was washed with EtOAc (35 mL), concentrated and resuspended in EtOAc (10 mL), and diluted with saturated solution of Na_2CO_3 (2 mL). The organic layer was separated and the aqueous layer was washed first with EtOAc (2 × 50 mL) then with $CHCl_3$/EtOH (4:1, 2× 30 mL). The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered and concentrated. Product **13** was isolated by flash column chromatography: the column was run with a gradient of EtOAc/ MeOH (100:0 and 98: 2) to afford 0.18 g (69%) of compound **217** as a yellow liquid which darkened when exposed to air.

Compound **13:** R_f = 0.18 in EtOAc/MeOH (95:5); IR (film) ν = 3061, 2977, 2939, 1634, 1582, 1478, 1434, 1400 cm^{-1}; ^1H NMR ($CDC1_3$, 300 MHz) δ: 9.14-

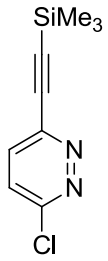
minor rotamer (d, *J* = 1.8 Hz,1H), 9.10-**major rotamer** (t, *J* = 1.8 Hz,1H), 7.35-7.48 (m, 2H), 6.17 (s, 1H), 6.09 (q, *J* = 7.2 Hz, 1H), 4.35 (t, *J* = 9.3 Hz, 2H), 2.92-**major rotamer** (s, 3H), 3.51 (s,2H), 2.76-**minor rotamer** (s, 3H), 2.63 (t, *J* = 9.3 Hz, 2H), 1.79-**minor rotamer** (d, *J* = 2.5 Hz, 3H), 1.68-**major rotamer** (d, *J* = 2.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 170.9, 161.8, 150.6, 142.4, 126.7, 107.8, 70.1, 51.9, 32.3, 32.2, 30.4, 15.3.; HRMS-EI calcd for $C_{13}H_{17}N_3O_2$: 247.1315, found 247.1320.



Synthesis of 1,2,5,6-tetrahydro-1,2-dimethyl-4H-furo[3,2-e]isoquinolin 3(7aH)-one (222):

In a flame-dried, Ar-flushed sealed tube, compound **217** (0.02 g, 0.08 mmol) was injected, then 1,2,4-trichlrobenzene (3 mL, 0.04 M) was added under an argon atmosphere. The sealed tube was evacuated and backfilled with argon (this procedure was repeated three times). The reaction mixture was kept at 190 ºC for 26 h in a sealed tube under an argon atmosphere. Product **222** was isolated by flash column chromatography: first EtOAc/hexane (1:9, 50 mL) was used as an eluent to remove 1,2,4-trichlrobenzene, then a gradient of EtOAc/MeOH (100:0 and 98:2) was used to afford 0.01g (58%) of compound **222** as a yellow oil.

Compound **222:** R_f = 0.33 in EtOAc/MeOH (95:5); IR (film) ν = 3042, 2979, 2871, 1644, 1487, 1447, 1400, 753 cm^{-1}; ^1H NMR ($CDC1_3$, 300 MHz) δ: 6.04-5.98-**major diastereoisomer** (m, 1H), 5.81-5.80-**minor diastereoisomer** (m, 1H), 5.79-5.72(m, 2H), 4.32-**major diastereoisomer** (d, *J* = 3.3 Hz), 4.31-**major diastereoisomer** (d, *J* = 3.3 Hz), 4.22-4.19-**major diastereoisomer** (m, 1H), 4.18-4.01-**minor diastereoisomer** (m, 1H), 3.77-3.69-**major diastereoisomer** (m, 2H), 3.67-3.56-**minor diastereoisomer** (m, 2H), 3.00 (s, 3H), 2.48-2.26-**major diastereoisomer** (m, 2H), 2.00-2.04 (m, 2H), 1.49-1.46-**minor diastereoisomer** (d, *J* = 4.8 Hz, 2H), 1.43-1.41-**major diastereoisomer** (d, *J* = 4.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 169.5, 141.7, 125.1, 123.5, 122.2, 116.5, 115.4, 82.1, 81.3, 63.41, 60.11, 56.5, 43.8, 42.0, 38.2, 32.4, 32.3, 23.0, 20.4; HRMS-EI calcd for $C_{13}H_{17}NO_2(M^+)$: 219.1259, found 219.1252; Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81; found C, 71.01; H, 7.95.

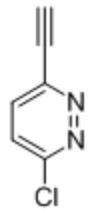


Synthesis of 3-chloro-6-(trimethylsilyl)ethynyl)pyridazine (236):

A 25 mL flame-dried round-bottomed flask equipped with a magnetic stir bar, rubber septa, and an argon inlet was charged with freshly distilled THF (2 mL), 3-chloro-6-iodopyridazine (0.20 g, 0.84 mmol) and cooled to 0 ºC via an ice bath.

To this solution triethylamine (0.70 mL, 5.04 mmol) was added and allowed to stir for 5 min followed by addition of trimethylsilylacetylene (0.13 mL, 0.92 mmol), copper (I) iodide (0.08 g, 0.04 mmol), and $PdCl_2(PPh_3)_2$ (0.03 g, 0.04 mmol). The reaction was allowed to stir at 0 °C for 1 h then warmed to room temperature and stirred until consumption of the starting material was observed via TLC (~ 4 h). When complete, the mixture was filtered through a celite plug and washed with ethyl acetate (30 mL). The filtrate was concentrated *in vacuo* and the dark brown oil was subjected to column chromatography (hexane:ethyl acetate, 9:1) affording 0.141 g of 3-chloro-6-((trimethylsilyl)ethynyl)pyridazine as a pale yellow oil and used for another step.

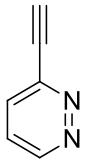
Compound **236:** R_f = 0.6 (hexane:ethyl acetate, 2:1); IR (film) ν = 3007, 2964, 1564, 1521, 1392, 1253, 1235, 1143, 862, 847 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 7.51 (q, J = 8.2 Hz, 2H), 0.28 (s, 9H); ^{13}C NMR (75 MHz; $CDCl_3$): δ 155.1, 146.8, 131.8, 127.5, 102.2, 99.3, -0.5; HRMS-EI Calcd for $C_9H_{11}N_2SiCl$ (M^+): 210.0380, Found: 210.0380.



Synthesis of 3-chloro-6-ethynylpyridazine (237):

A 10 mL flame dried round-bottomed flask equipped with a magnetic stir bar, rubber septum, and argon inlet was charged with freshly distilled THF (3.7 mL) and crude of 3-chloro-6-(trimethylsilyl)ethynyl pyridazine (0.09 g, 0.46 mmol). To this solution TBAF (0.70 mL, 1 M in THF, 0.70 mmol) was added and the solution turned dark red. The reaction was immediately quenched with saturated ammonium chloride (5 mL) and the aqueous layer was extracted with ethyl acetate (3 x 20 mL). The organic layers were combined, dried with sodium sulfate, filtered, and concentrated *in vacuo* affording a dark red oil. The oil was subjected to column chromatography (hexane: ethyl acetate, 4:1) affording 0.05 g (71% in two steps) of 3-chloro-6-ethynylpyridazine as a white solid yield.

Compound 237: 152 ºC (decompose, Et_2O); R_f = 0.3 (hexane:ethyl acetate, 2:1); IR (film) ν = 3621, 3302, 3011, 2962, 2928, 2873, 2125, 1731, 1565, 1530, 1520, 1450, 1392, 1301, 1148, 1067, 1046, 908 cm^{-1}; ^1H NMR (300 MHz; $CDCl_3$): δ 7.57 (d, *J* = 8.8 Hz, 1H), 7.51 (d, *J* = 8.8 Hz, 1H), 3.48 (s, 1H); ^{13}C NMR (75 MHz; $CDCl_3$): δ 155.7, 146.2, 131.9, 127.7, 83.3, 78.9; HRMS-EI Calcd for $C_6H_3ClN_2$ (M^+): 137.9985, Found: 137.9985. Anal. Calcd for $C_6H_3ClN_2$: C, 41.13; H, 4.55; found C, 41.20; H, 4.69.

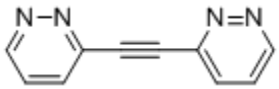


Synthesis of 3-Ethynylpydridazine (239):

A flame dried round-bottomed flask equipped with a magnetic stir bar, rubber septum, and an argon inlet was charged with freshly distilled THF (50 mL), 3-iodopyridazine (1.68 g, 8.20 mmol), $PdCl_2(PPh_3)_2$ (0.28 g, 0.41 mmol), copper (I) iodide (0.08 g, 0.41 mmol) and triethylamine (3.43 mL, 24.60 mmol). The suspension was stirred and degassed using a stream of argon for 15 minutes. To this solution trimethylsilylacetylene (1.51 mL, 10.66 mmol) was added dropwise and the reaction was allowed to stir for 12 h. The mixture was filtered through a Celite plug and washed with methylene chloride (30 mL). The filtarate was washed with 10 mL sat. solution of ammonium chloride. The aqueous layer was extracted twice with 20 mL of methylene chloride. The organic layers were combined, concentrated *in vacuo* affording a dark brown oil which was dissolved in 20 mL of THF and treated with a tetrabutylammonium fluoride solution (12.30 mL, 1 M in THF, 12.30 mmol) at 0 °C (under an argon atmosphere). After 10 min the reaction mixture was treated with 20 mL sat. solution of ammonium chloride and 50 mL methylene chloride. The mixture was transferred to a separatory funnel and the aqueous layer was separated from the organic layer. The aqueous phase was extracted three times with 20 mL portions of methylene chloride. The organic layers were combined, washed with brine, and dried over Na_2SO_4. The

solvent was removed *in vacuo* and subjected to flash column chromatography (hexane: ethyl acetate, 4:1 to 1:1) to afford 710 mg of 3-ethynylpyridazine (82%) as a white solid which turned to a yellow powder when exposed to air.

Compound **239:** 124-126 ºC (hexane:ethyl acetate); R*f* = 0.1 (hexane:ethyl acetate, 1:1); IR (film) *v* 3307, 3005, 2120, 1569, 1423, 1369, 1231, 1072, 1009, 812, 655 cm^{-1}; ^{1}H NMR (300 MHz; $CDCl_3$): δ 9.15 (dd, *J* = 5.0, 1.6 Hz, 1H), 7.61 (dd, *J* = 8.5, 1.7 Hz, 1H), 7.48 (dd, *J* = 8.5, 5.0 Hz, 1H), 3.44 (s, 1H); ^{13}C NMR (75 MHz; $CDCl_3$): δ 149.9, 147.3, 129.9, 125.7, 81.9, 79.9; HRMS-EI Calcd for $C_6H_4N_2$ (M+): 104.0374, Found: 104.0374.

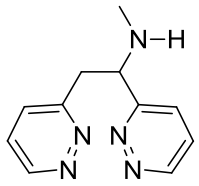


Synthesis of 1,2-di(pyridazin-3-yl)ethyne (240):

A flame dried round-bottomed flask equipped with a magnetic stir bar, rubber septum, and an argon inlet was charged with freshly distilled THF (10 mL), 3-iodopyridazine (0.37g, 1.82 mmol), copper (I) iodide (0.01 g, 0.076 mmol), $PdCl_2(PPh_3)_2$ (0.05 g, 0.076 mmol), and triethylamine (0.64 mL, 4.56 mmol). The suspension was stirred and degassed using a stream of argon for 15 minutes. To this solution 3-ethynylpyridazine (0.21 g, 2.00 mmol) in 2 mL of THF was added dropwise and the reaction was allowed to stir for 12 h. The mixture was filtered through Celite and the filter plug was washed with methylene chloride (30 mL). The mother liquor was concentrated *in vacuo* and the product was isolated by

flash column chromatography: silica-gel was neutralized with a mixture of EtOAc/Hexane (1:4) with 5% TEA and column was run with an eluent of EtOAc/Hexane (1:4), EtOAc (100%) and EtOAc/MeOH/TEA (99:5:0.5) to afford 241 mg of 1,2-di(pyridazin-3-yl)ethyne as a pale yellow solid (59%) which turned to yellow-brown solid when exposed to air.

Compound **240:** 187 ºC (ether)/(decomposed); R_f = 0.1 (ethyl acetate); IR (film) ν = 2967, 2637, 2467, 1599, 1577, 1443, 1226, 1086, 1023 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 9.24 (t, J = 2.5 Hz, 1H), 7.82 (dd, J = 8.4, 1.3 Hz, 1H), 7.57 (dt, J = 8.6, 4.4 Hz, 1H); ^{13}C NMR (75 MHz; $CDCl_3$): δ 150.1, 147.2, 130.2, 125.9, 89.1; HRMS-EI Calcd for $C_{10}H_6N_4$ (M+): 182.0592, Found: 182.0592.

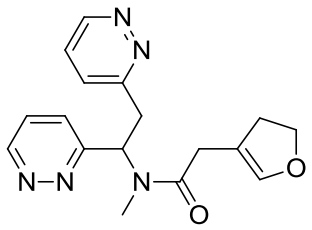


Synthesis of *N*-methyl-1,2-di(pyridazin-3-yl)ethanamine (241):

In a flame-dried, Ar-flushed sealed tube, 1,2-di(pyridazin-3-yl)ethyne (0.15g, 0.82 mmol) was added and cooled externally to -50 ºC. $Ti(NMe_2)_4$ (0.2 M solution in toluene, 0.41mL, 0.08mmol) in 2.5 mL toluene was added in a seal tube and the reaction mixture was bubbled with excess methylamine gas for 5 min. The sealed tube was capped and allowed to warm to room temperature with stirring in a span of 20 min. The flask was placed in an oil bath and heated externally to 37 °C for 40 min and then allowed to cool to room temperature. The reaction was cooled to

-10 ºC and argon was bubbled through until methylamine was no longer detected by Alkacid paper. A mixture of $NaBH_3CN$ (0.10g, 1.65 mmol) and $ZnCl_2$ (0.11g, 0.82 mmol) in methanol (6 mL) was added at rt and stirred for 20 h. Methylene chloride (20 mL) and a saturated Na_2CO_3 solution (10 mL) were added. The resulting mixture was filtered and the solid residue was washed with methylene chloride (50 mL). After extraction, the organic layer was separated. The aqueous layer was extracted with methylene chloride (5 × 20 mL) and the combined organic layers were dried with Na_2SO_4, filtered, and concentrated. Flash column chromatography: the column was run with $CHCl_3$/Et_2NH (0 to 5%) then $CHCl_3$/Et_2NH/MeOH (95:3:2) to afford 0.11g (41%) dark yellow oil (compound **241)** which turned dark brown in colour after some time.

Compound **241**: R*f* = 0.24 (25% Et_2NH in $CHCl_3$); IR (film) ν = 3691, 3338, 3025, 2994, 2857, 2802, 1602, 1582, 1556, 1478, 1435, 1397, 12341106, 1083, 1013 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 9.10 (d, *J* = 4.9 Hz, 1H), 9.06 (d, *J* = 4.6 Hz, 1H), 7.61 (d, *J* = 8.3 Hz, 1H), 7.44 (dd, J_1 = 8.3, J_2 = 4.9 Hz, 1H), 7.38-7.28 (m, 2H), 4.45 (t, *J* = 6.8 Hz, 1H), 3.52-3.45 (m, 2H), 2.3 (s, 1H) ; ^{13}C NMR (75 MHz; $CDCl_3$): δ 164.4, 160.9, 150.6, 149.9, 127.5, 126.6, 126.4, 126.0, 64.2, 42.4, 34.4; HRMS-EI Calcd for $C_{11}H_{13}N_5$ (M+): 215.1175, Found: 215.1171.



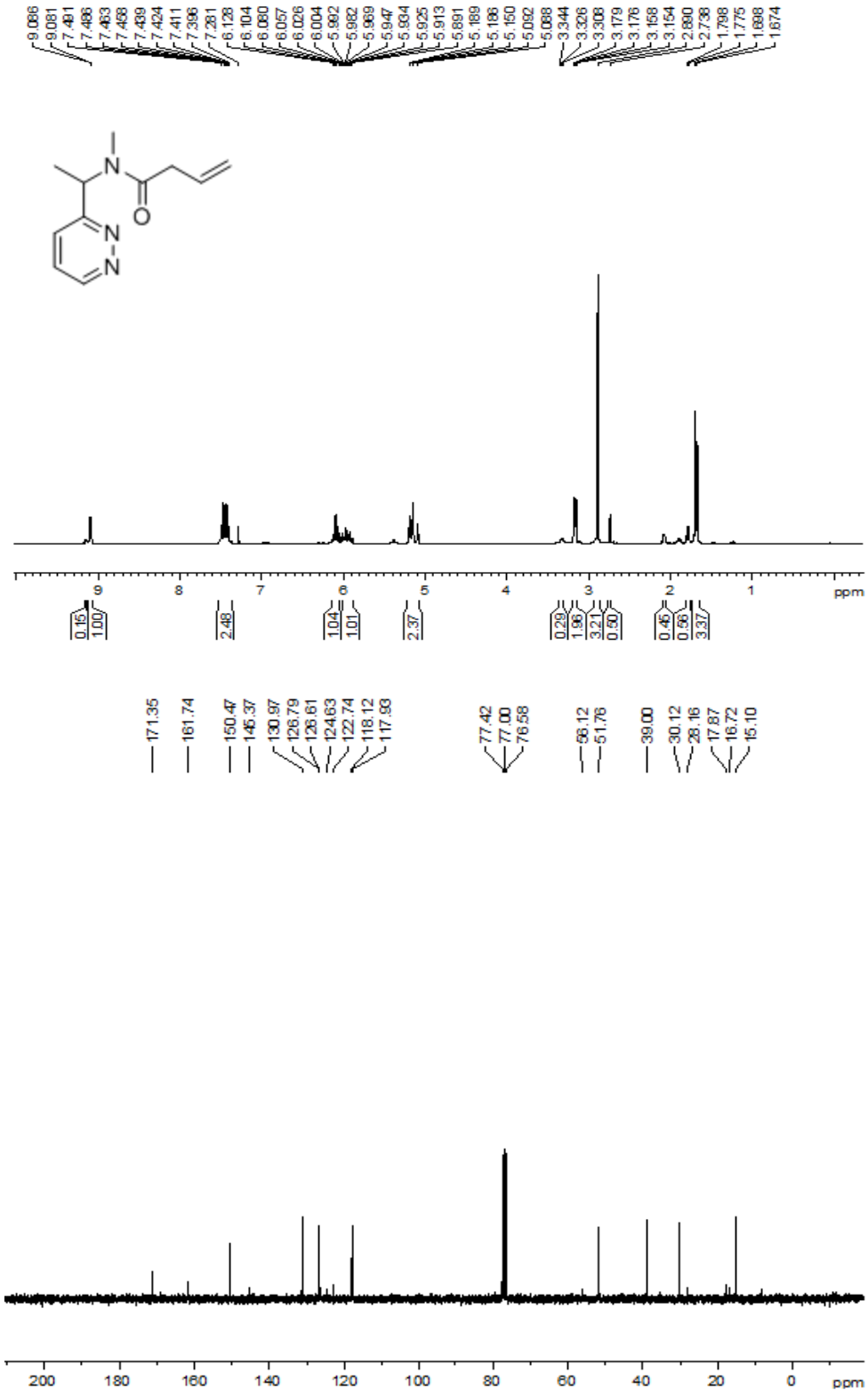
N-(1,2-di(pyridazin-3-yl)ethyl)-2-(4,5-dihydrofuran-3-yl)-N-methylacetamide (234):

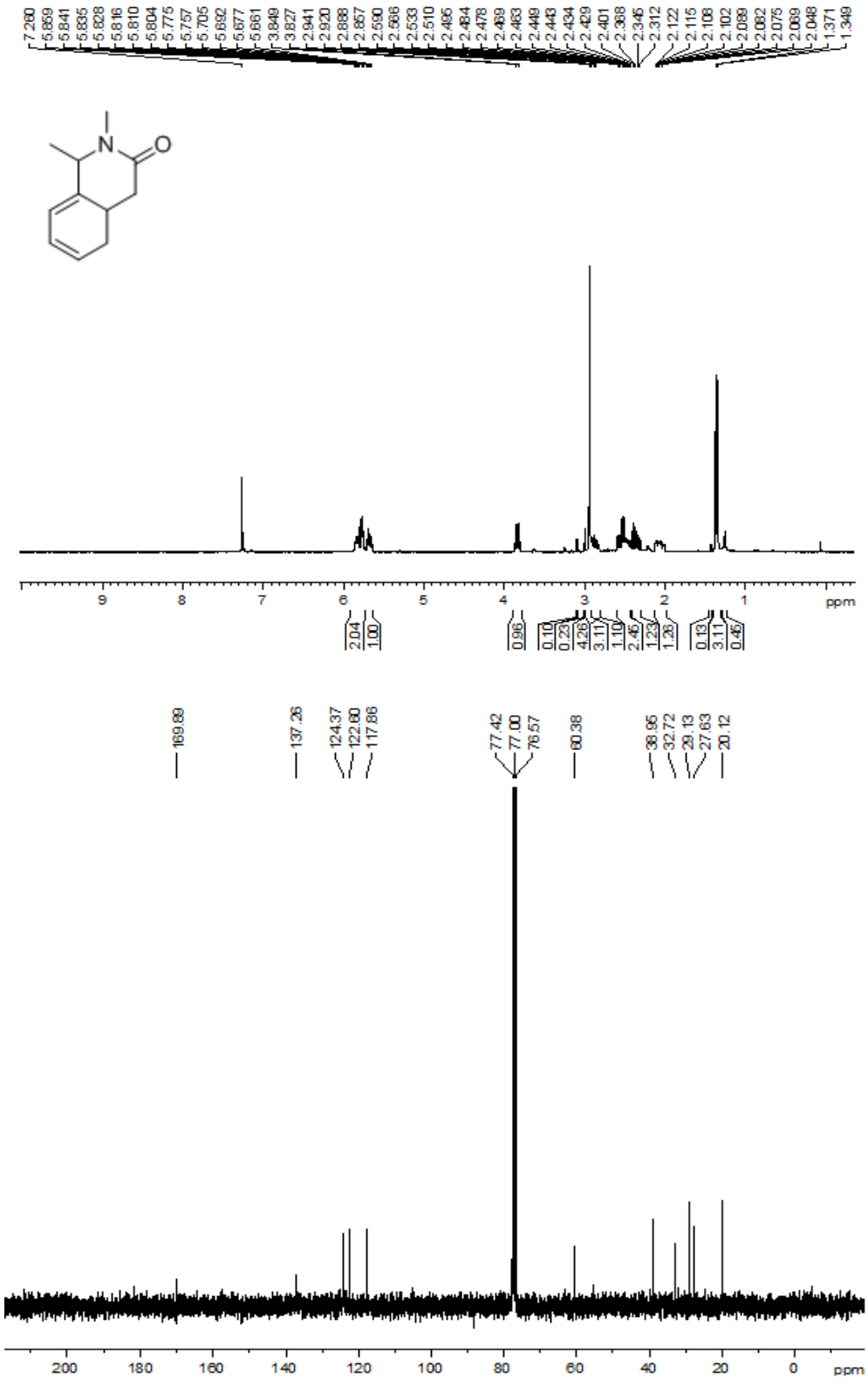
To a flame-dried, argon-flushed round-bottomed flask was added compound **241** (0.06g, 0.28 mmol) in DMF (2 mL). Activated molecular sieves (4 Å) were introduced at < 10 ºC and stirred for 10 min. Diisopropylethylamine (0.12 mL, 0.69 mmol), compound **12** (0.05 g, 0.42 mmol) and COMU (0.12 g, 0.28 mmol) were successively added. The reaction mixture was allowed to warm to room temperature with stirring and allowed to stir for another 14 h. The mixture was filtered through Celite and the filter plug was washed with methylene chloride (30 mL). The mother liquor was concentrated in rotawap then *in high vacuo* for 8 h to remove the DMF. Flash column chromatography: the column was run with $CHCl_3$/Et_2NH (0 to 5%) to afford 0.06g light brown oil compound **234** (73%) which turned dark brown in colour after some time.

Compound **234:** R*f* = 0.42 (25% Et_2NH in $CHCl_3$);); IR (film) ν = 3696, 3001, 2957, 2924, 2853, 1642, 1604, 1583, 1396, 1266, 1095, 1013, 871 cm^{-1}; ^1H NMR ($CDC1_3$, 300 MHz) δ: 9.14 (dd, J_1 = 3 Hz, J_2 = 4.8 Hz,1H), 9.10 (dd, J_1 = 1.2 Hz, J_2 = 4.8 Hz,1H), 7.55-7.37 (m, 4H), 6.58-**major rotamer** (dd, J_1 = 3.6 Hz, J_2 = 9.3 Hz,1H), 6.22-**minor rotamer** (dd, J_1 = 7.5 Hz, J_2 = 15 Hz,1H), 6.02 (s, 1H),

4.28 (m, 2H), 3.01 (s, 1H), 2.99-**major rotamer** (s, 3H), 2.76-**minor rotamer** (s, 3H),2.64-**minor rotamer** (m, 2H), 2.39-**major rotamer** (m, 2H);^{13}C NMR (75 MHz; $CDCl_3$): δ171.4, 160.4, 160.3 150.9, 149.9, 142.5, 127.1, 127.0, 126.9, 126.3, 107.45, 70.11, 56.05, 35.62, 32.14, 31.88, 31.06; HRMS-EI Calcd for $C_{17}H_{19}N_5O_2$ (M+): 325.1529, Found: 325.1538.

VI. Selected Spectra

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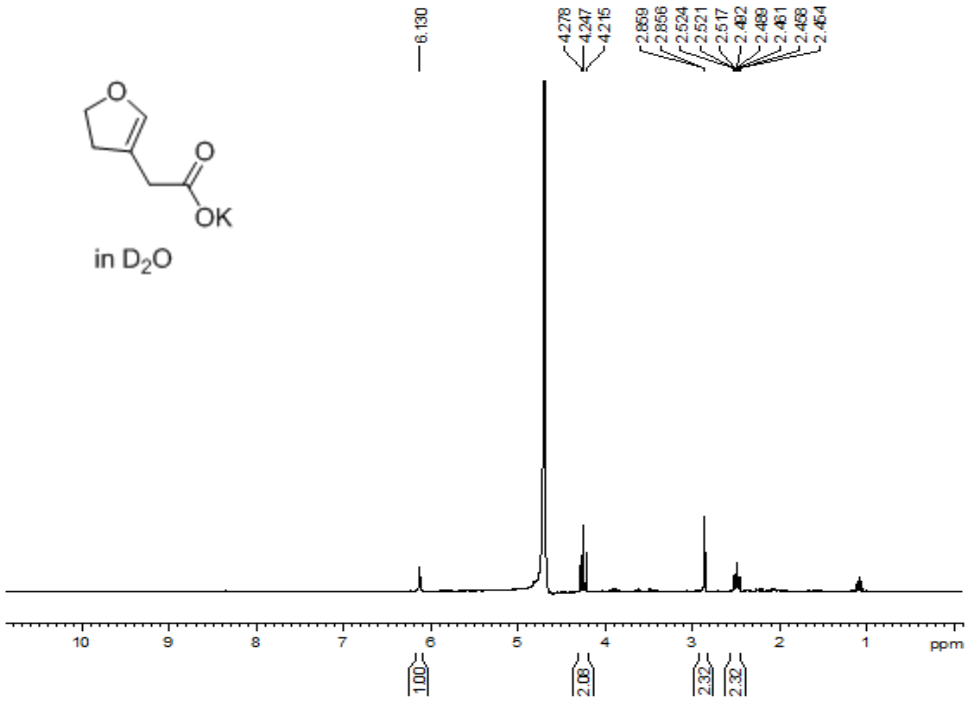
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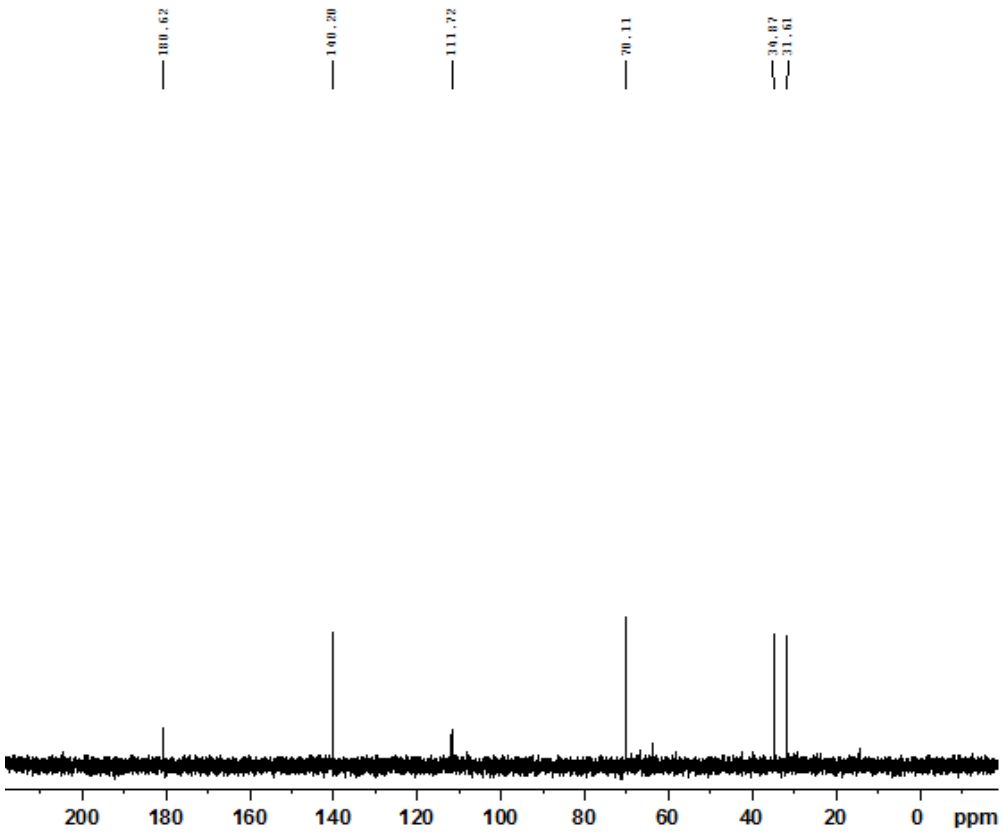
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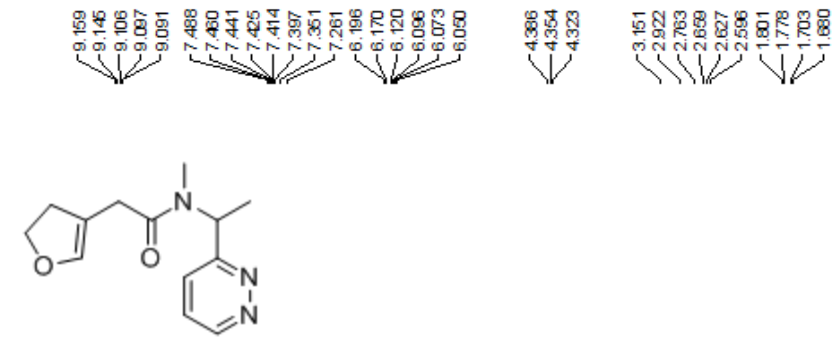
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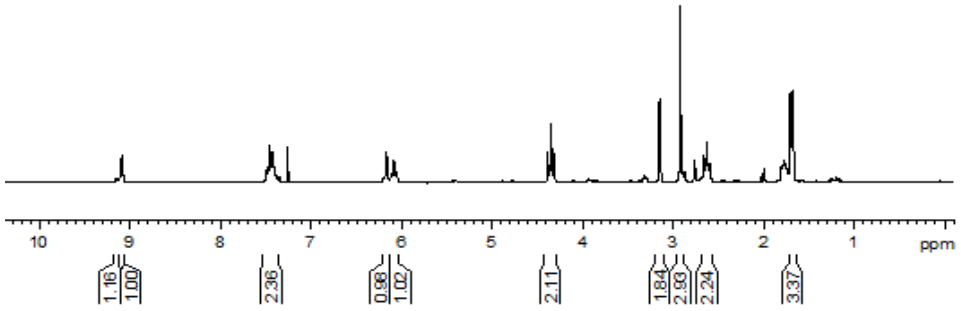
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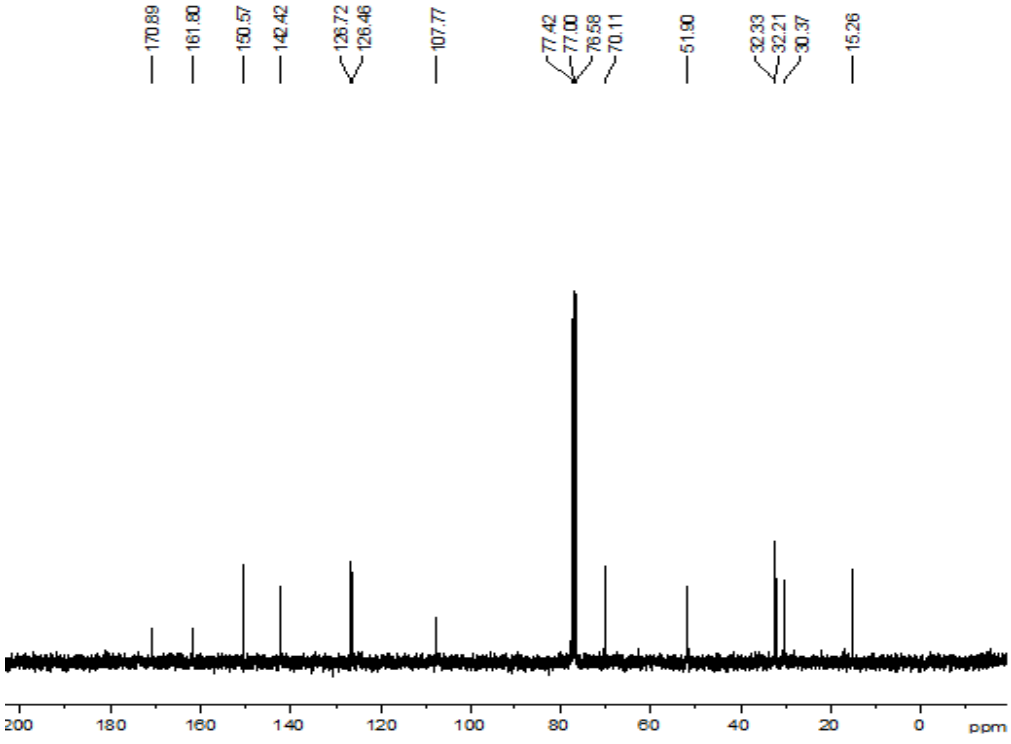
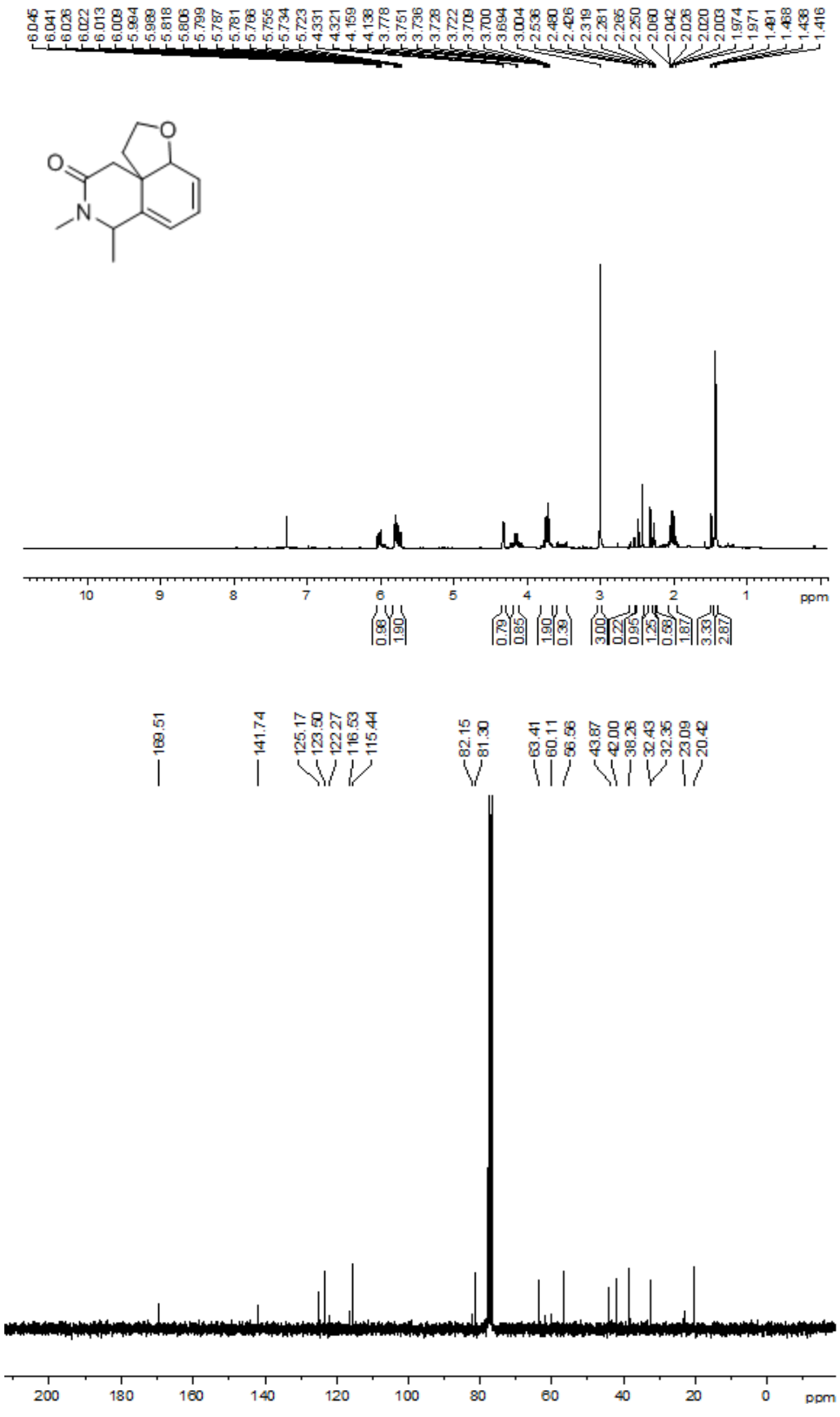
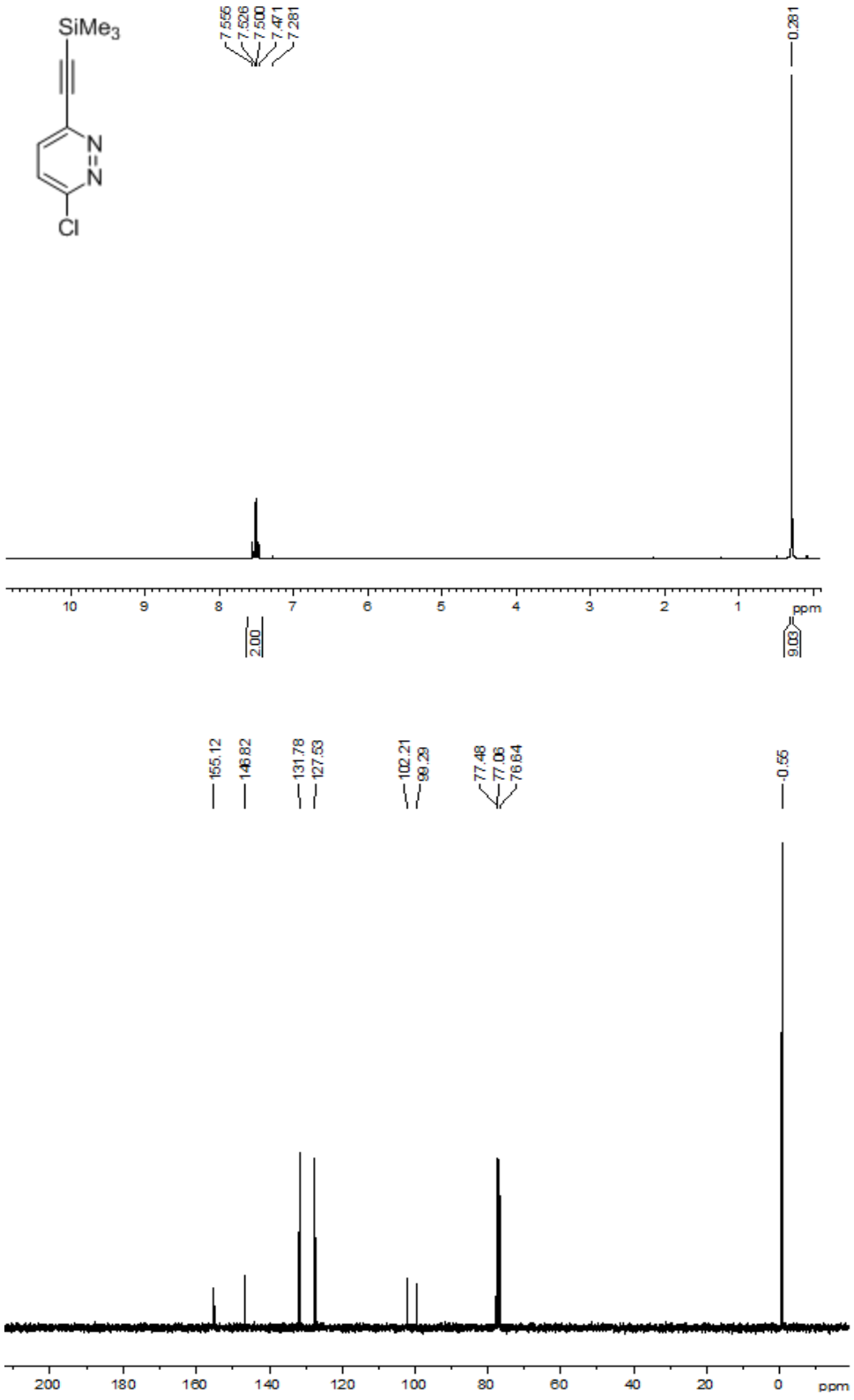
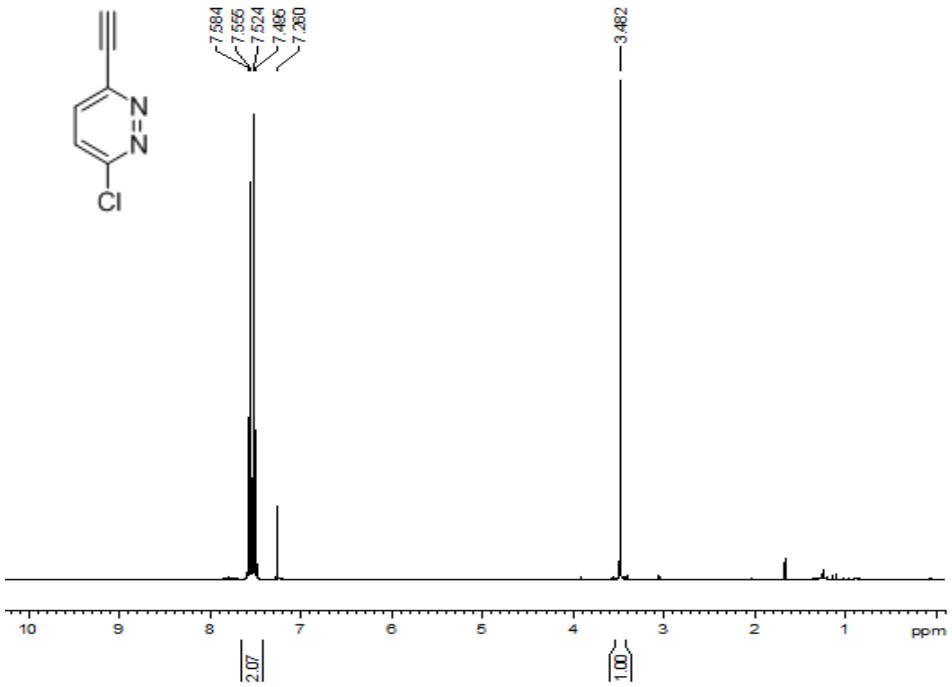
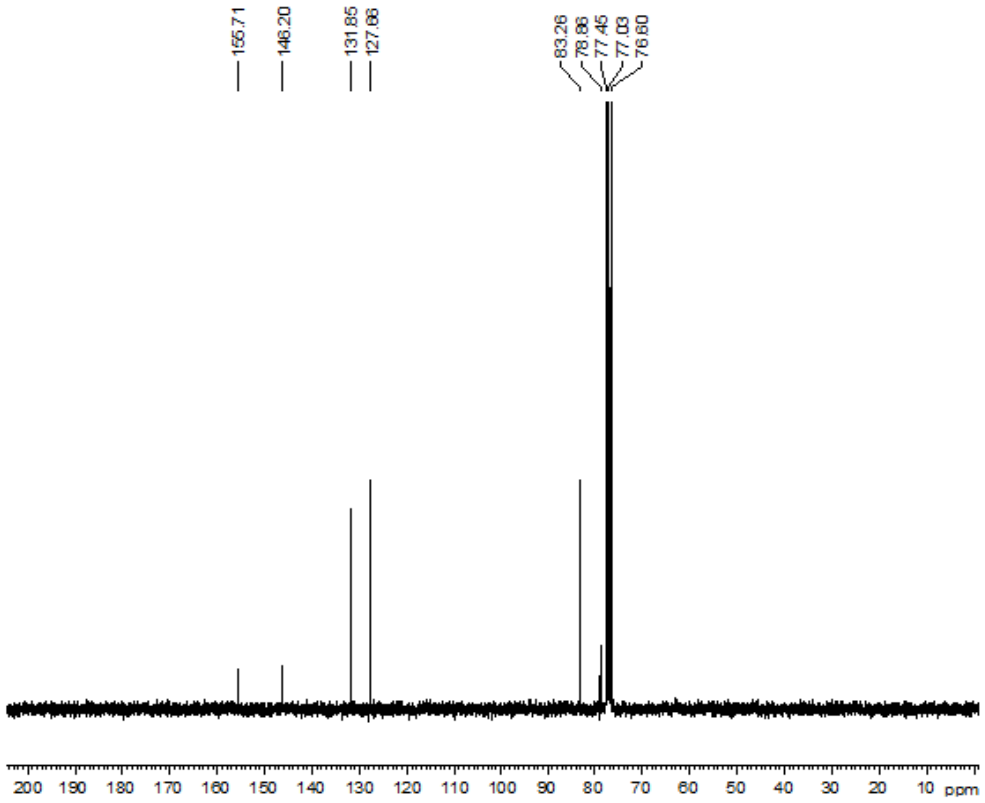
3.37

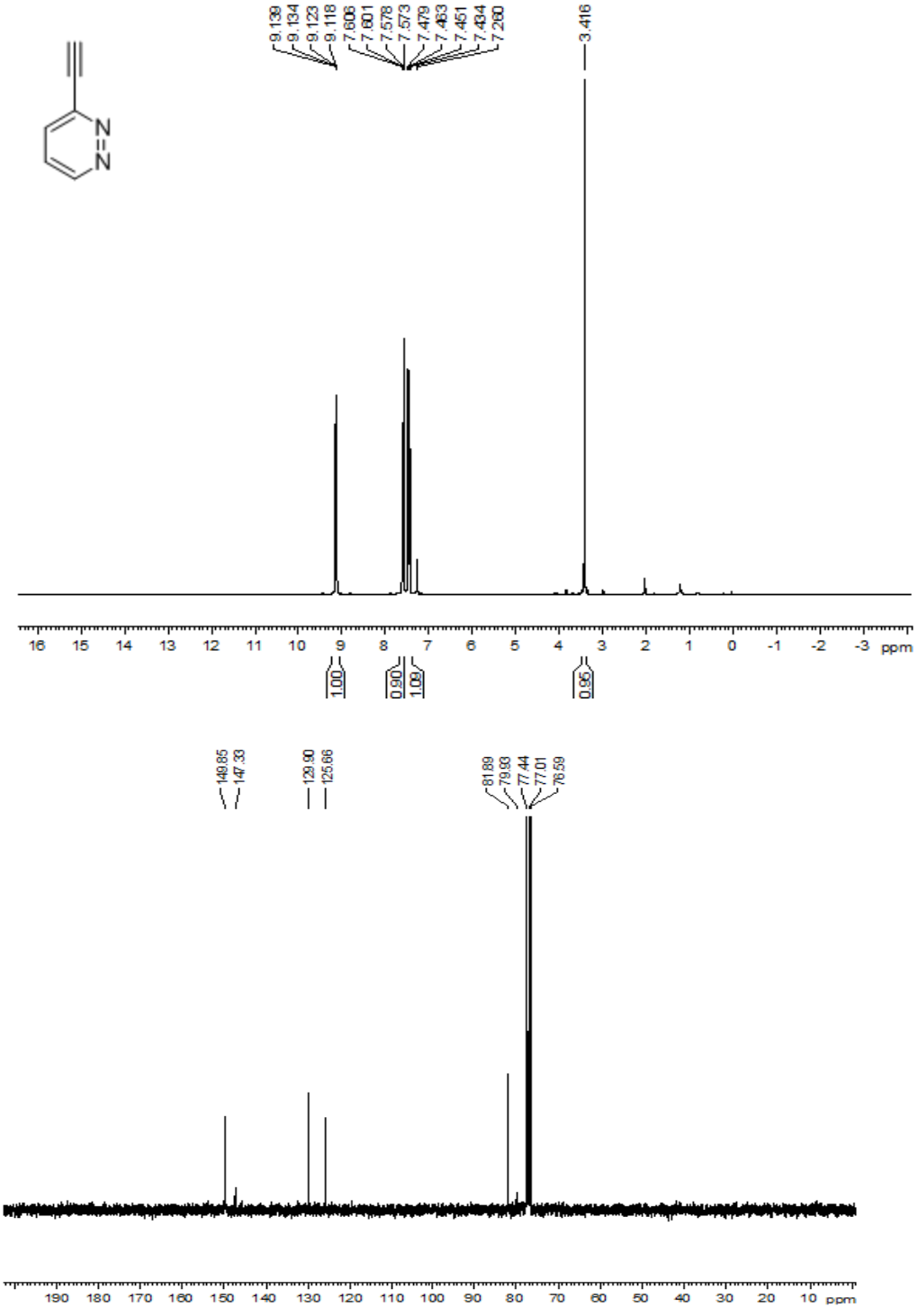

170.89
161.80
150.57
142.42
126.72
126.46
107.77
77.42
77.00
76.58
70.11
51.90
32.33
32.21
30.37
15.26
200
180
160
140
120
100
80
60
40
20
0
ppm

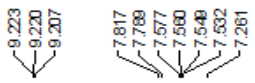

6.045
6.041
6.026
6.022
6.013
6.009
5.994
5.989
5.818
5.806
5.799
5.787
5.781
5.766
5.755
5.734
5.723
4.331
4.321
4.159
4.138
3.778
3.751
3.736
3.728
3.722
3.709
3.700
3.694
3.004
2.536
2.480
2.426
2.319
2.281
2.265
2.250
2.060
2.042
2.026
2.020
2.003
1.974
1.971
1.491
1.488
1.438
1.416
O
O
N
10
9
8
7
6
5
4
3
2
1
ppm
0.98
1.90
0.79
0.85
1.90
0.39
3.00
0.22
0.95
1.25
0.99
1.87
3.33
2.87
169.51
141.74
125.17
123.50
122.27
116.53
115.44
82.15
81.30
63.41
60.11
56.66
43.87
42.00
38.26
32.43
32.35
23.09
20.42
200
180
160
140
120
100
80
60
40
20
0
ppm

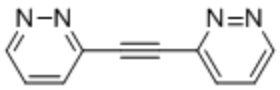

SiMe3
N
N
Cl
7.555
7.526
7.500
7.471
7.281
0.281
10
9
8
7
6
5
4
3
2
1
ppm
2.00
9.03
155.12
146.82
131.78
127.53
102.21
99.29
77.48
77.06
76.64
-0.55
200
180
160
140
120
100
80
60
40
20
0
ppm

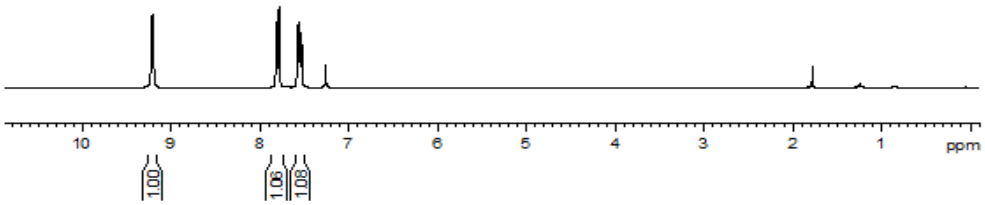

7.584
7.555
7.524
7.495
7.260
3.482
N
N
Cl
10
9
8
7
6
5
4
3
2
1
ppm
2.07
1.00

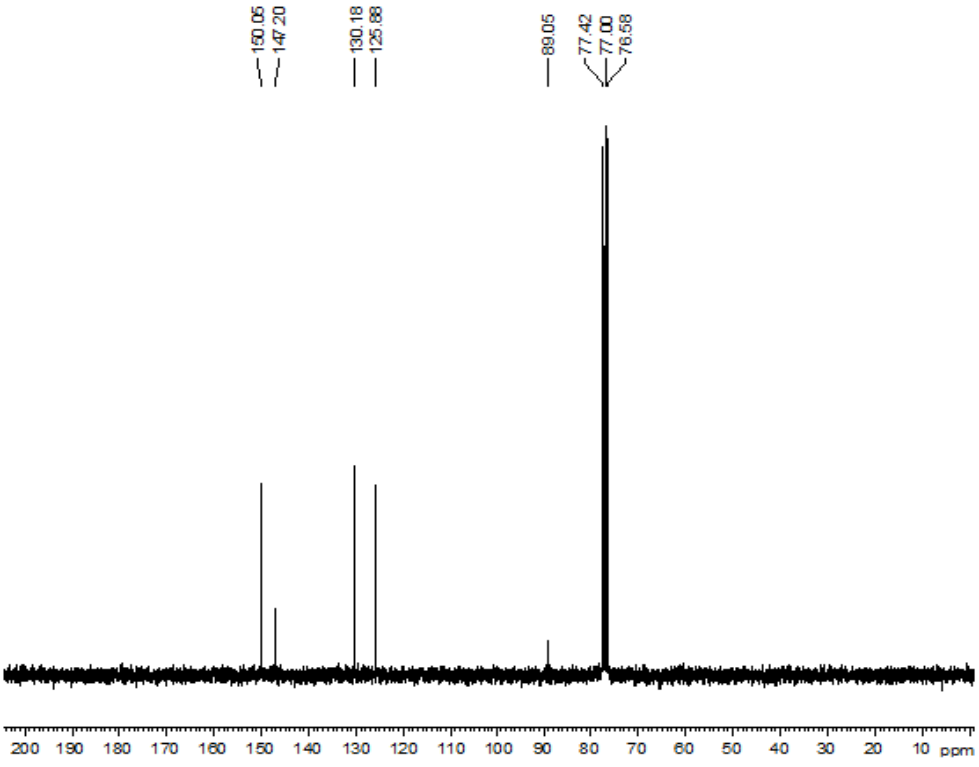

155.71
146.20
131.85
127.86
83.26
78.86
77.45
77.03
76.60
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

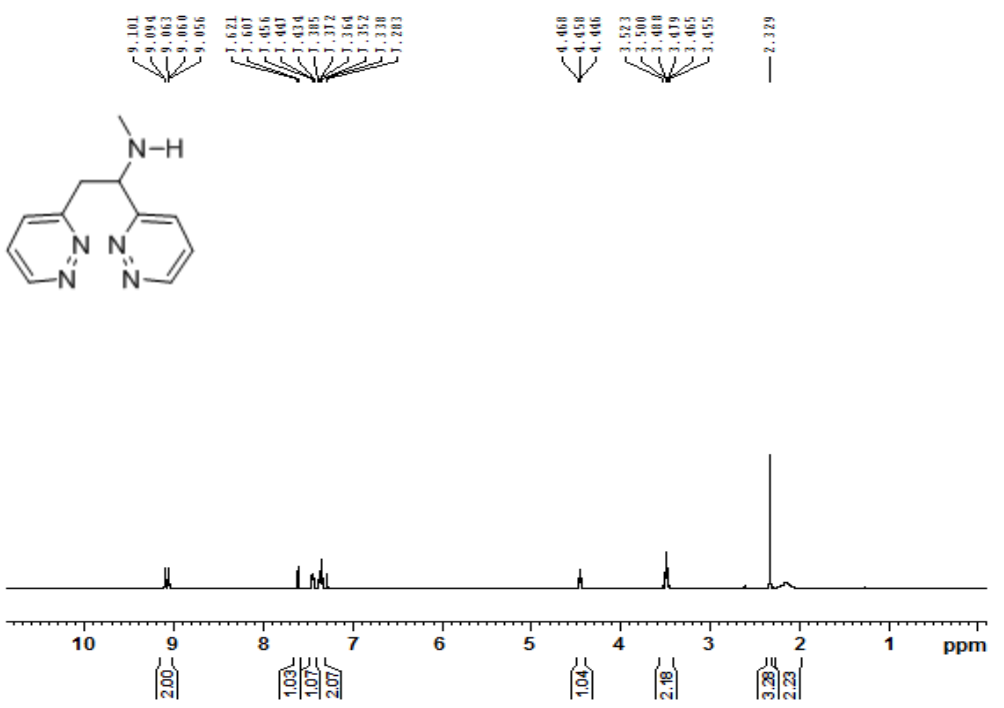

9.139
9.134
9.123
9.118
7.606
7.601
7.578
7.573
7.479
7.463
7.451
7.434
7.260
3.416
16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2 -3 ppm
1.00
0.90
1.09
0.95
149.85
147.33
129.90
125.66
81.89
79.93
77.44
77.01
76.59
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

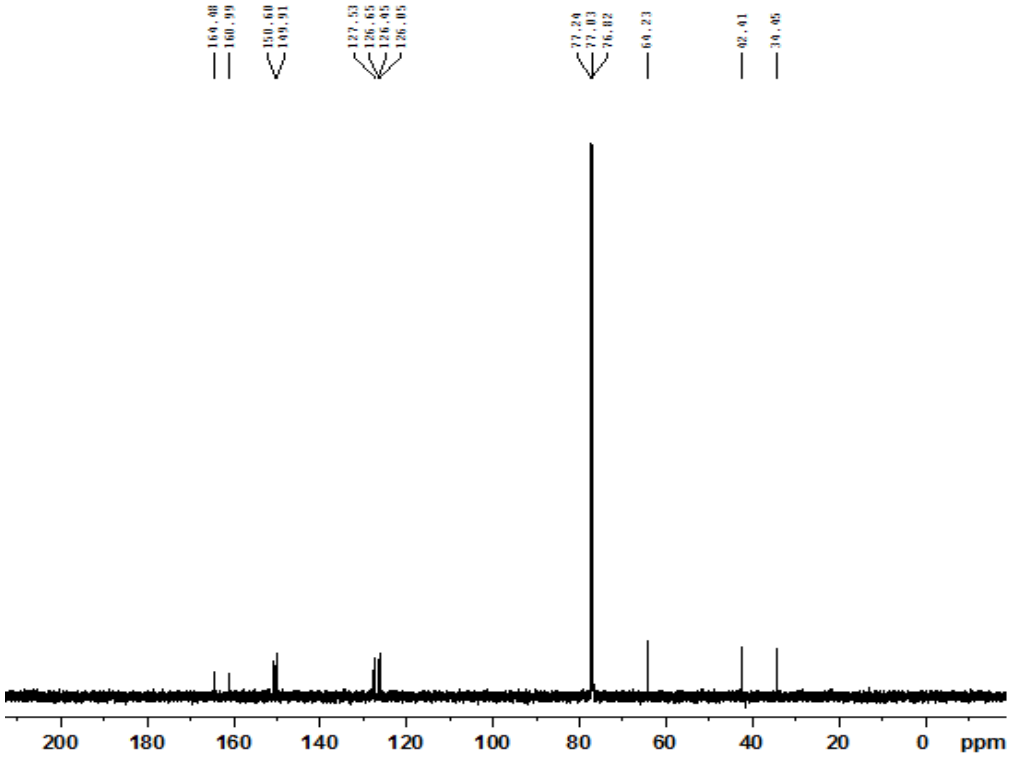

9.223
9.220
9.207
7.817
7.789
7.577
7.560
7.549
7.532
7.261

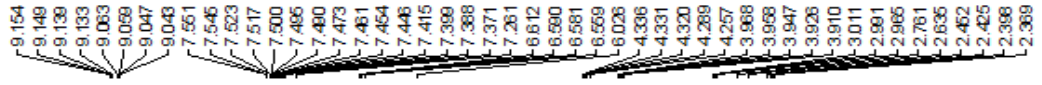

N–N
N=N

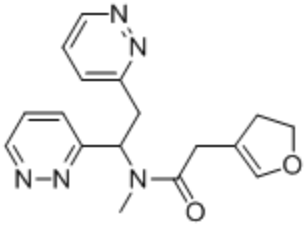

10
9
8
7
6
5
4
3
2
1
ppm
1.00
1.08
1.08

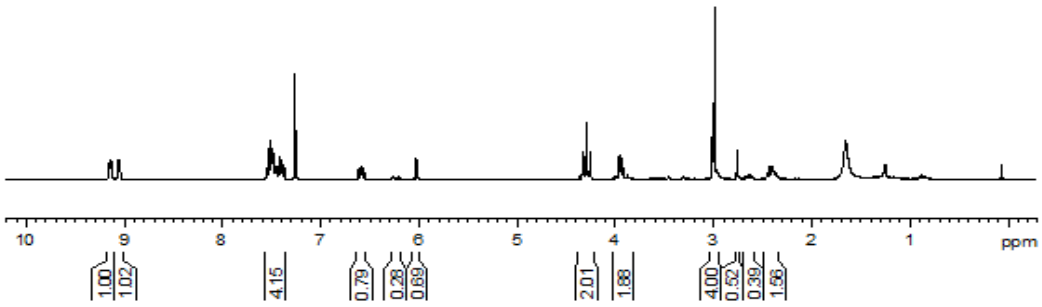

150.05
147.20
130.18
125.88
89.05
77.42
77.00
76.58
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

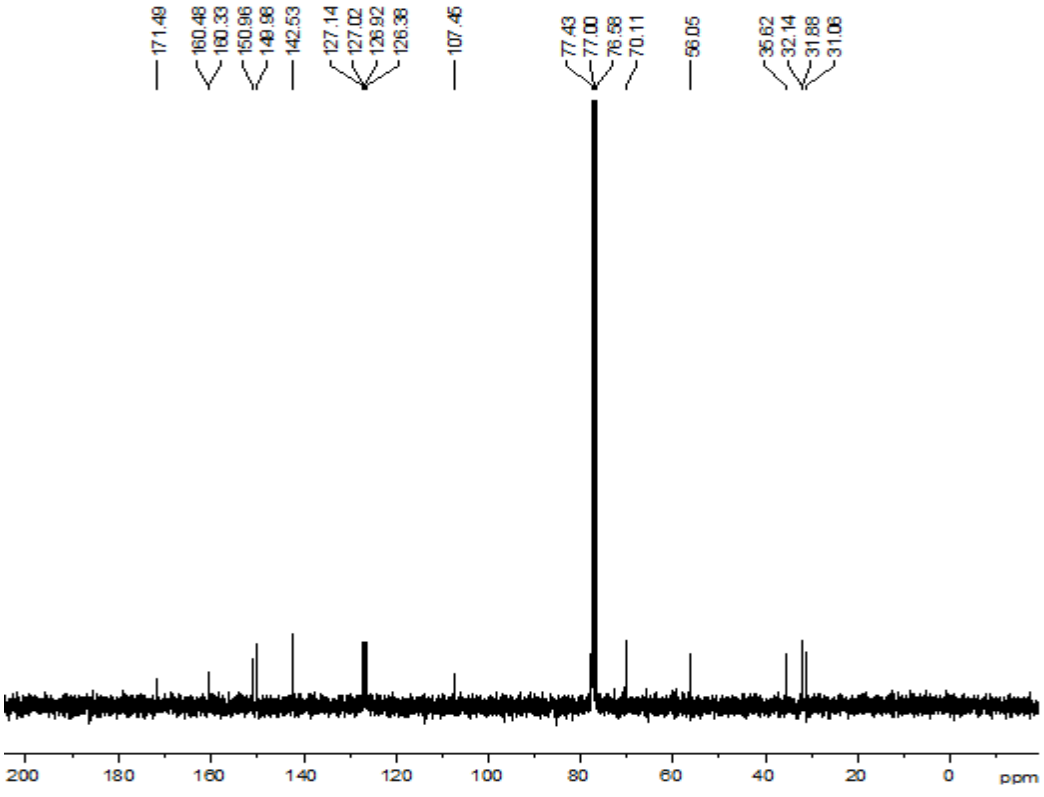

9.101
9.094
9.063
9.060
9.056
7.621
7.607
7.456
7.447
7.434
7.385
7.372
7.364
7.352
7.338
7.283
4.468
4.458
4.446
3.523
3.500
3.488
3.479
3.465
3.455
2.329
N–H
N
N
N
N
10
9
8
7
6
5
4
3
2
1
ppm
2.00
1.03
1.07
2.07
1.04
2.18
3.28
2.23


169.08
160.99
150.60
149.91
127.53
126.65
126.45
126.05
77.24
77.03
76.82
60.23
42.41
34.46
200
180
160
140
120
100
80
60
40
20
0
ppm


9.154
9.149
9.139
9.133
9.063
9.059
9.047
9.043
7.551
7.545
7.523
7.517
7.500
7.495
7.480
7.473
7.461
7.454
7.446
7.415
7.399
7.388
7.371
7.261
6.612
6.590
6.581
6.559
6.026
4.336
4.331
4.320
4.289
4.257
3.968
3.958
3.947
3.926
3.910
3.011
2.991
2.965
2.761
2.635
2.452
2.425
2.398
2.369




10
9
8
7
6
5
4
3
2
1
ppm
1.00
1.02
4.15
0.79
0.28
0.69
2.01
1.88
4.00
0.52
0.39
1.56


171.49
160.48
160.33
150.96
149.98
142.53
127.14
127.02
126.92
126.38
107.45
77.43
77.00
76.58
70.11
66.05
35.62
32.14
31.88
31.06
200
180
160
140
120
100
80
60
40
20
0
ppm

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VIII. Vita

Setu Gupta was born and raised in Kanpur, Uttar Pradesh, India in 1988. He and his younger brother, Tushar, were raised by their parents, Umesh and Vineeta.

He attended 'Pandit Deen Dayal Vidalaya' High School in Kanpur, India before moving on to university studies at Manipal University in Manipal, India. After graduating in 2011 he moved to St. Catharines, Ontario to begin his graduate studies under the supervision of Professor Tomas Hudlicky at Brock University.

He is presently working towards the completion of his M.Sc. in chemistry. His research interests include the total synthesis towards the synthesis of thebaine.